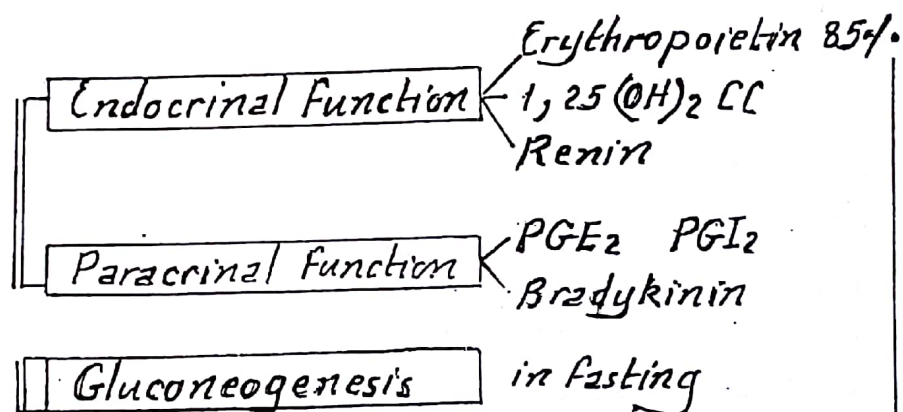
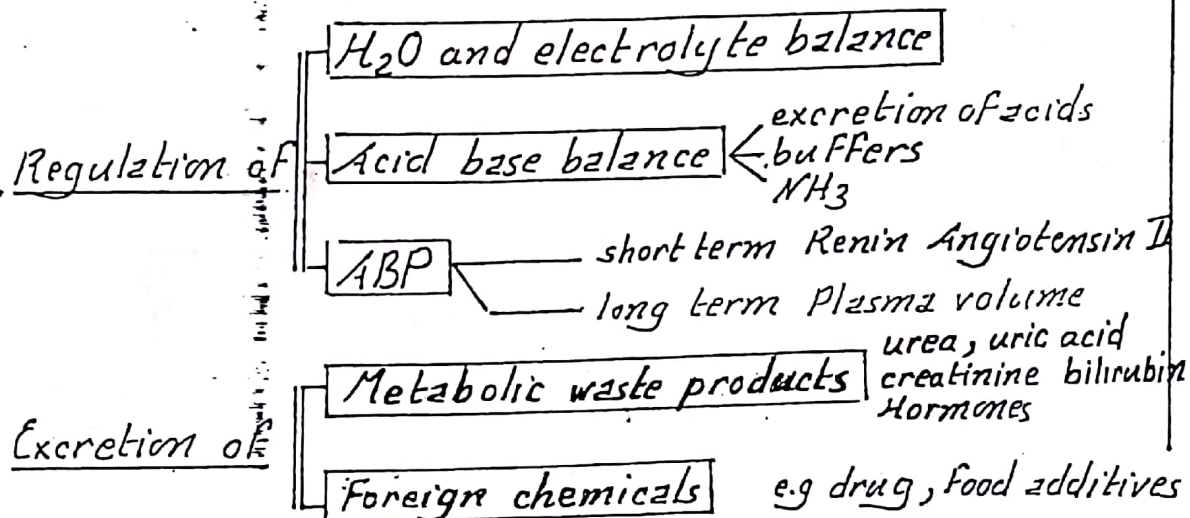


"KIDNEY"

Functions

Major HOMEOSTATIC Function



Physiologic anatomy

Weight : 150 gm

Size : Clinched fist

< 12cm x < 8cm

Two major regions :

- Cortex granular deeper

- Medulla striated paler

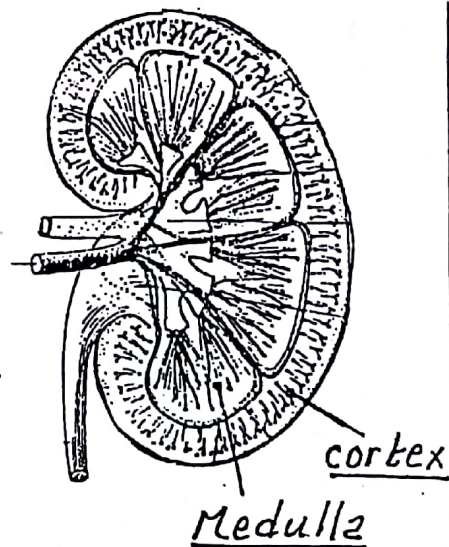
is divided into pyramids

pyramid → renal papilla

→ minor calyx → major calices

→ pelvic → ureter

N.B Calyces, pelvis & ureter have smooth muscles



VISIT...

LANZAROTE
Caliente.COM

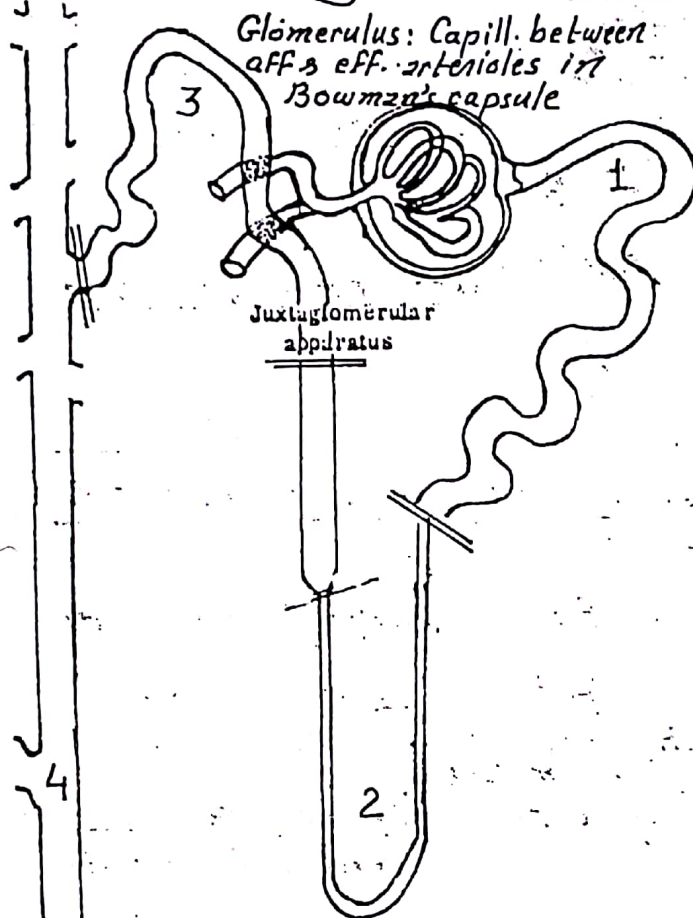
Microscopic anatomy

Each kidney contains 1.3 million

Functional unit

nephron

Glomerulus
Tubule



1 PCT single layer 15 mm
Apex: tight junction
brush border
mitoch
lateral intercell space

2 Loop of Henle
Thin Thick
Flat epith Cuboidal cells.
Descending & 1/2 ascend

3 DCT

5 mm
No brush border
few microvilli

4 Collecting T. 20 mm
2 types of cells

N.B Glomerulus, PCT & DCT are located in renal cortex

Principal cells P cells

Intercalated cells I cells

1 Predominant cells

Less number

2 Less microvilli
mitochondria
vesicles

More

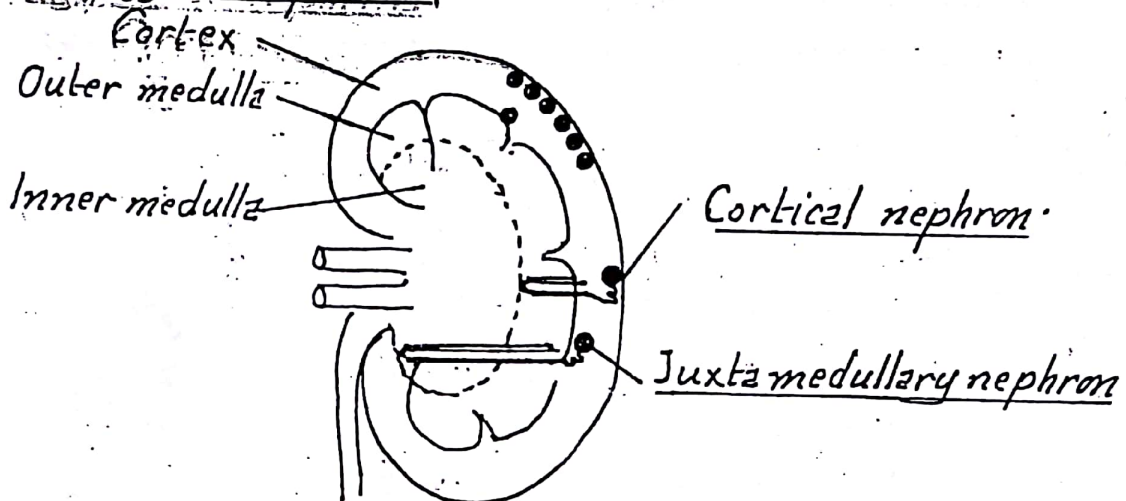
3 Functions

- Na^+ - K^+ exchange
via aldosterone
- H_2O reab ADH

Functions

- Acid secretion
- HCO_3^- reabsorption (2)

Types of nephrons



	Cortical nephron	Juxtamedullary n.
1 % of total	85%	15%
2 Glomerulus	Outer part of cortex	Inner part of cortex
3 Loop of Henle	Short: dips to junction between inner & outer medulla	Long: dips to pyramids
4 Blood supply	Peritubular capill.	Vasa recta & Peritubular capill.
5 Specific function		Urine concentration

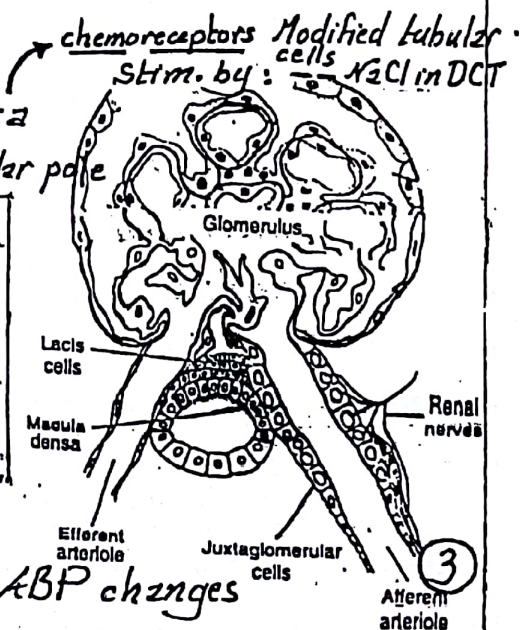
Juxta glomerular apparatus

Area of contact between

- Distal tubules: ^{1st part} Macula densa
- Afferent & Efferent arterioles: At vascular pole

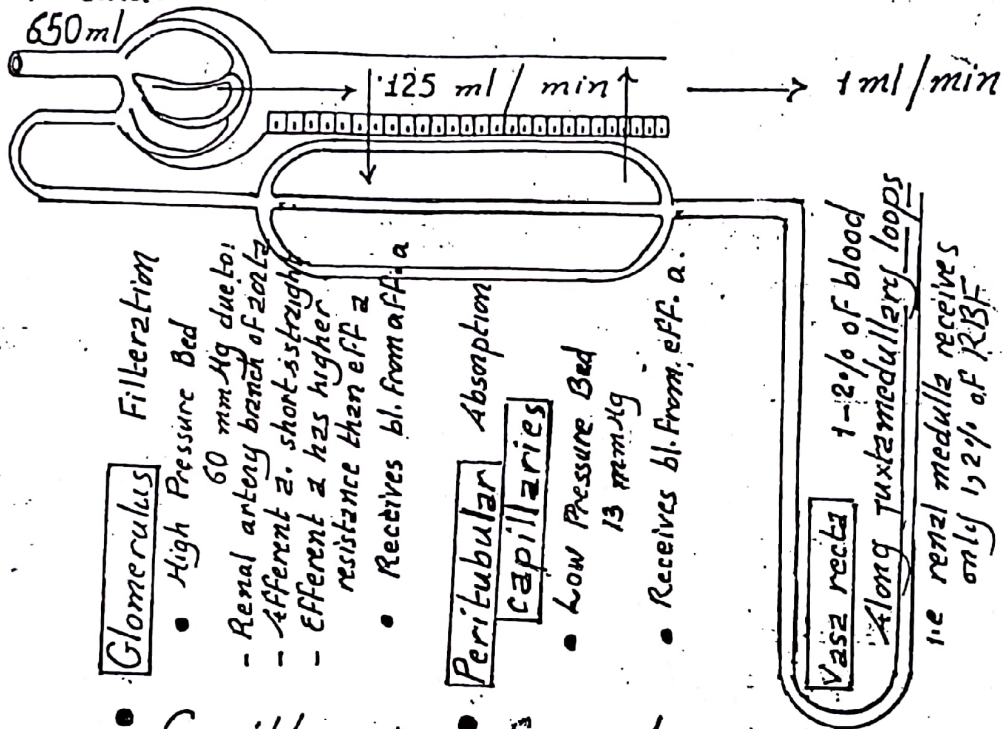
Juxtaglomer. cells	Lacis cells
1 Granular	Aggranular
2 Medial of aff.	Between aff & eff arterioles
3 Secrete renin	Stores renin

Function Autoregulation
 GFR RBF
 of same nephron.



Renal blood flow RBF 20-25% of COP i.e. 1.2-1.3 L/min

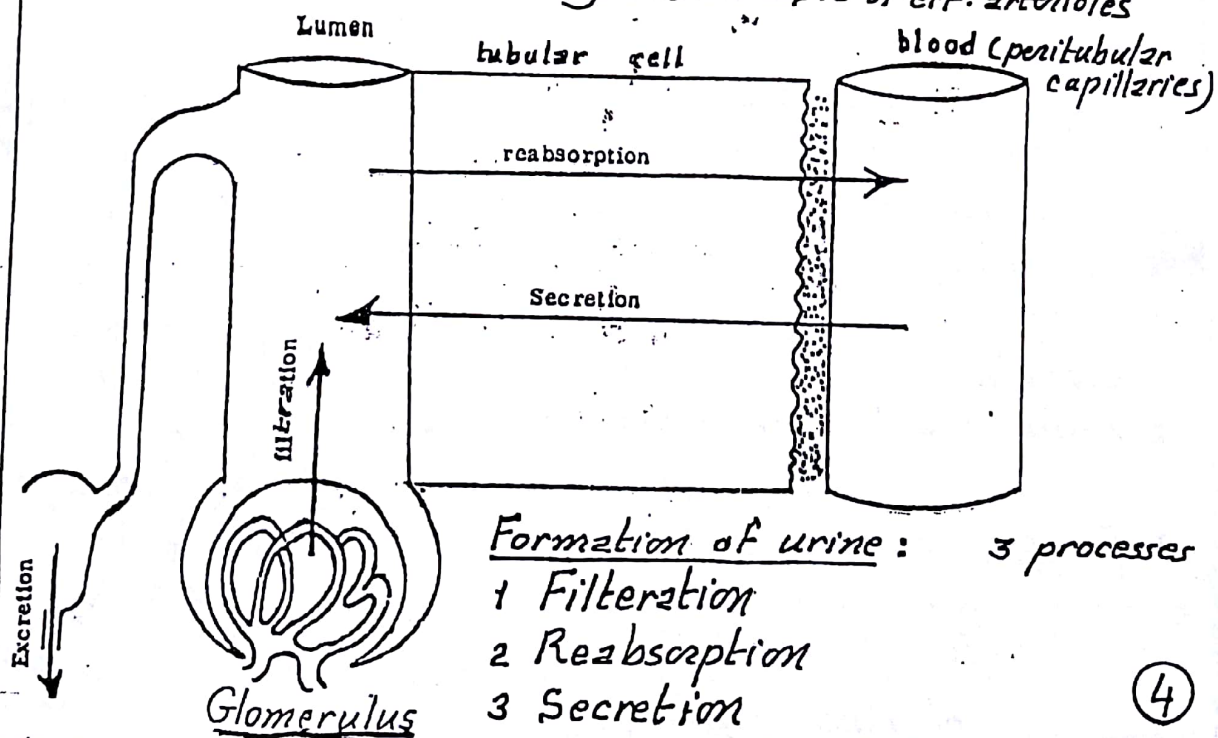
Renal artery → interlobar a → interlobular a → aff. arterioles
 → Glomerulus → eff. arteriole → peritubular capill. & vasa recta
 plasma.



• Capillaries of nephrons

Autoregulation of RBF between ABP 90-220 mm Hg

- 1 At high pressure: Intrinsic myogenic response.
 ++ ABP → stretch aff. arteriole → ++ Ca^{2+} influx → direct VC → ± RBF
- 2 At low pressure: a tubuloglomerular feedback. Discuss
 ↓ Angiotensin II → VC of eff. arterioles



Glomerulus

Glomerular filtrate is a ptn free ultrafiltrate

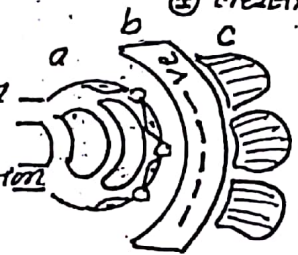
- Composition Plasma - colloids (ptn)
- Volume $\sigma \cdot 125 \text{ ml / min.}$ $\phi 10\% \text{ less}$
 7.5 L / hour
 $180 \text{ L / day (60 times plasma vol.)}$
 $> 99\% \text{ of GFR is reabsorbed}$

$$\text{Filtration Fraction} = \frac{\text{GFR}}{\text{RBF}} = \frac{125}{650} = 20\%$$

- Glomerular membrane
 $\text{NB} \rightarrow \text{GFR} \rightarrow \text{++ plasma creatinine}$ $\text{Aging} \rightarrow \text{RBF} \rightarrow \text{GFR} \rightarrow \text{++ creatinine}$
 $\text{muscle mass} \rightarrow \text{++ creatinine}$

- 3 layers

- a Capill endoth. holes 79-90 nm
- b Basement mem +ve charges
 $\text{barrier against plasma ptn filtration}$
- c Podocytes (pseudopodia) $\text{slit pores } 25 \text{ nm}$



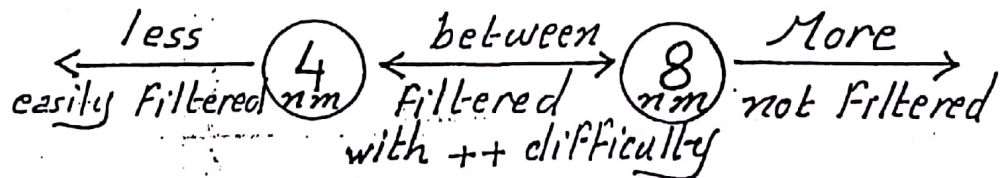
Mesangial cells

- Stellate cells
- Between basement mem & endothelium at bifurcat
- Contractile cells $\xrightarrow{\text{contract}}$ reduce filtrat. area
- Takes up immune complex $\rightarrow$ glomerular diseases

- Surface area 0.8 m^2

- Permeability 50 times sk. ms capillary
 It is highly selective and depends on:

[a] Size of molecules:



[b] Charges of molecules:

-ve charged < +ve charged

Only 0.2% of albumin is filtered

N.B loss of -ve charges of basement mem $\rightarrow$ albuminuria 5

Measurement of GFR

Inulin clearance

Fructose MW 5200 (found in dahlia tubers)

- 1 Freely filtered i.e. plasma conc. = Filterate conc.
- 2 Not reabsorbed or secreted

So, Amount Filtered = Amount excreted

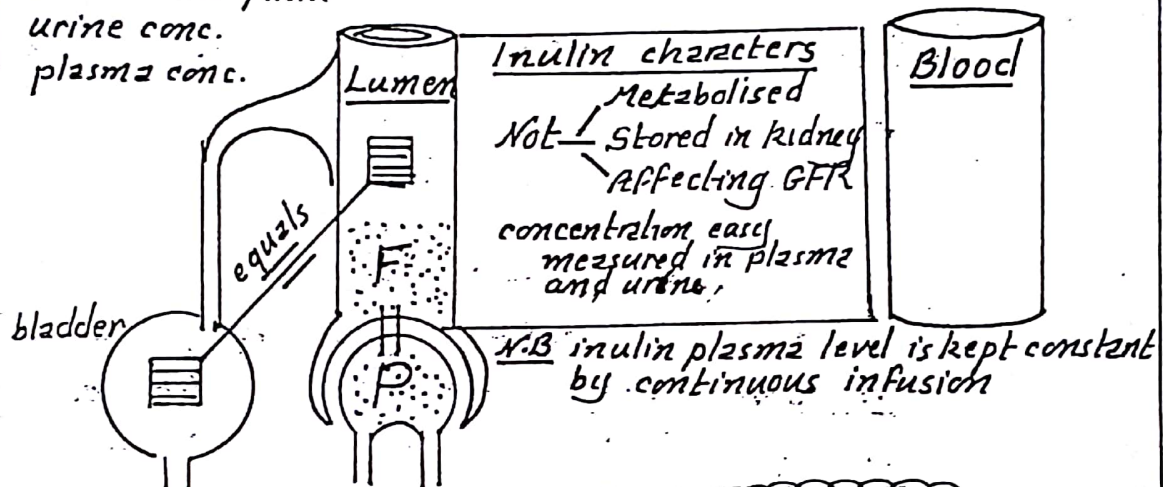
$$GFR \times P(F) = V \times U$$

$$GFR = \frac{V \times U}{P} = 125 \text{ ml/min.}$$

V - vol. of urine/min

U urine conc.

P plasma conc.



Creatinine clearance

Advantage: endogenous i.e. no extra work is added to diseased kidney

Radio isotopes

as ^{51}Cr EDTA

Disadvantage:

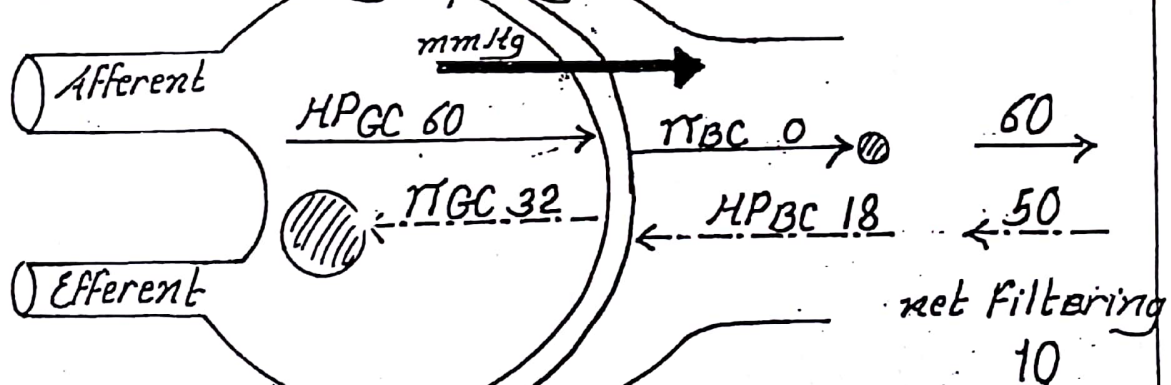
Creatinine is partially secreted so, $U \times V$ is high

However, P also is high due to non specific chromogen

So error is cancelled.

Forces that affect GFR

Same forces in any capillary



Starling equation

$$GFR \propto (HPGC + \pi BC) - (HPBC + \pi GC)$$

$$= K_f \text{ net filtering pressure}$$

K_f depend on [area permeability]

Glom. membrane

⑥

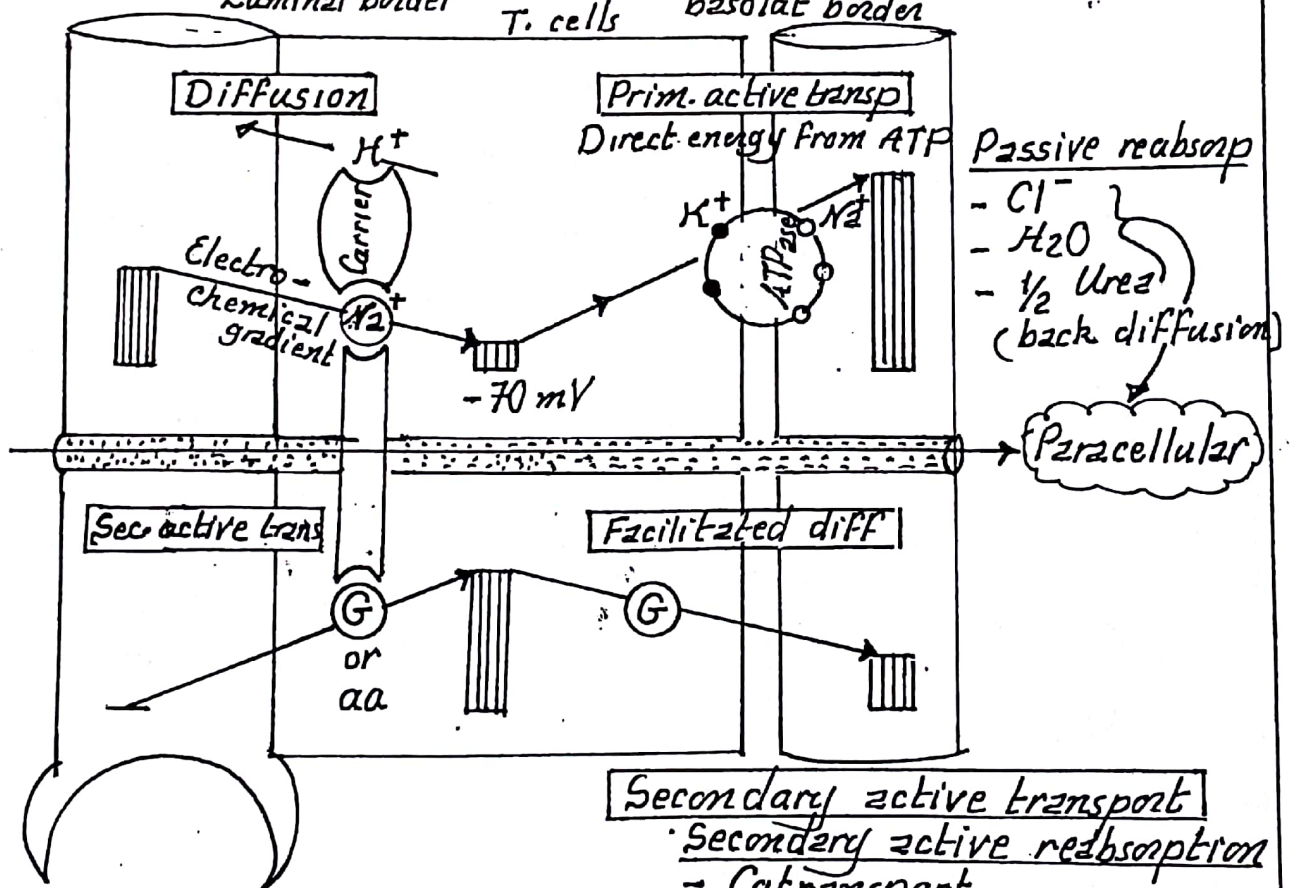
Urinary excretion rate = Filtrate rate - reabsorp. rate + secretion rate

Magnitude of tubular processing of glomerular filtrate

Substance	conc. in Urine (U)	conc. in plasma (P)	U/P ratio
Glucose mg/dl	0	100	0
Na^+ mEq/L	90	150	0.6
Urea mg/dl	900	15	60
Creatinine mg/dl	150	1	150

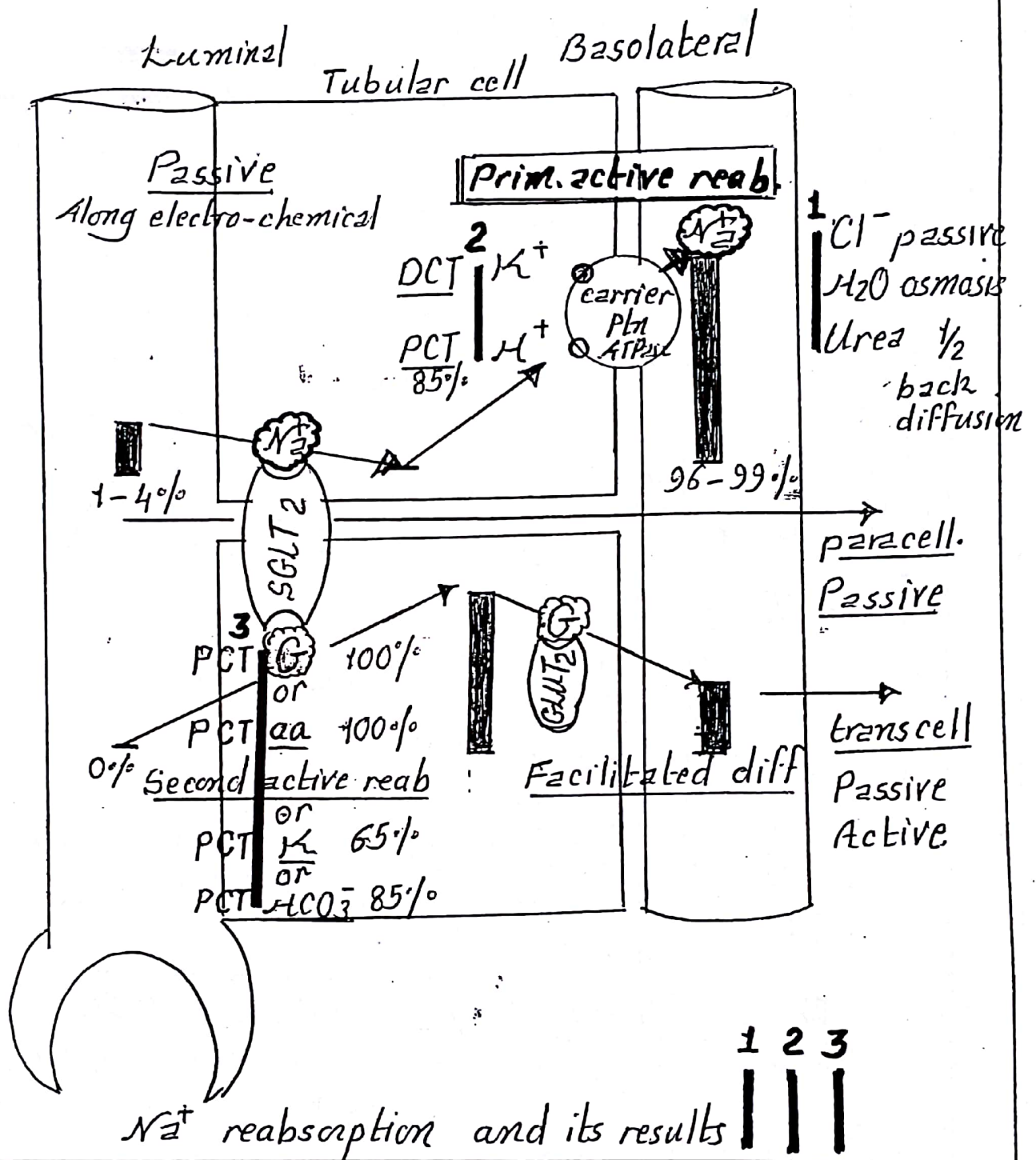
Mechanism of tubular transport

- 1 Paracellular inbetween cells
 - 2 Transcellular across cells
- Luminal border T. cells basolat border
- Passive → Active



Pinocytosis in PCT
Plns or peptides

Secondary active transport
Secondary active reabsorption
 = Cotransport
 e.g glucose or aa
Two substances in One direction
Secondary active secretion
 = Counter transport
 e.g H^+ or K^+
Two substances in Two directions



Pinocytosis 0.2 g% albumin

	H^+	K^+
<u>PCT</u>	second active <u>SECRETION</u>	second active reab
<u>DCT</u>	prim. active <u>SECRETION</u>	second active secretion 8%

Tubular transport maximum

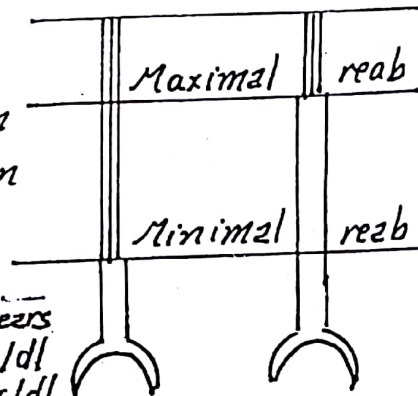
Substances actively reabsorbed or secreted.
require specific transport system (carrier - enzyme)
exhibit transport maximum (when it is saturated)

• T_m limited reabsorption

e.g. glucose, amino acids,
phosphate & sulphate

T_m G ♂ 375 mg/min
♀ 300 mg/min

Renal threshold
Plasma conc. above which substance appears
in urine
• venous 180 mg/dl
arterial 200 mg/dl



• T_m limited secretion

e.g. PAH, penicillin

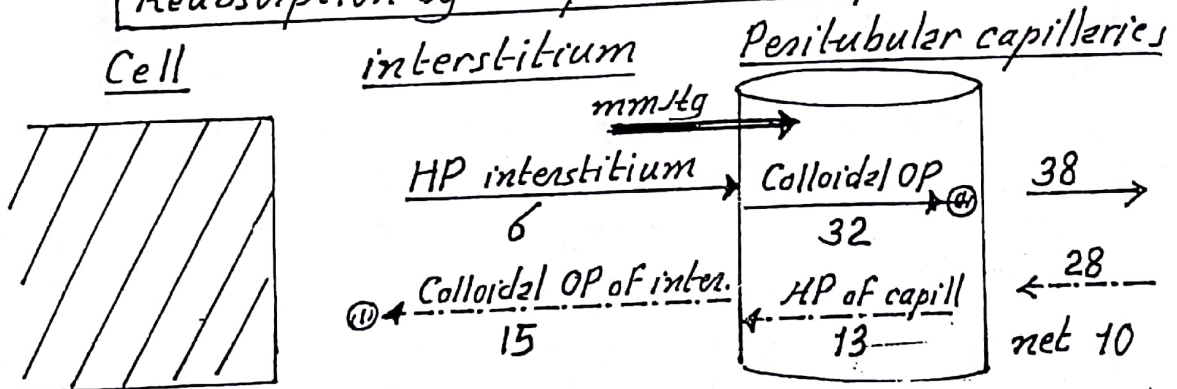
Affinity of transport substance for substance is high

Gradient time transport

Substances reabsorbed by diffusion.
DR & conc. gradient & time

Sodium is actively transported. However, in.
- PCT exhibits gradient time transport.
- DCT & collecting T. " T_m.

Reabsorption by the peritubular capillaries



$$\begin{aligned} \text{Net reabsorptive force} &= (32 + 6) - (13 + 15) \\ &= 38 - 28 \\ &= 10 \text{ mmHg} \end{aligned}$$

Na. handling by renal tubules

- 96-99% of Na^+ is actively reabsorbed except in THIN descending & ascending loop of H
- 90% of kidney energy for Na^+ reab.

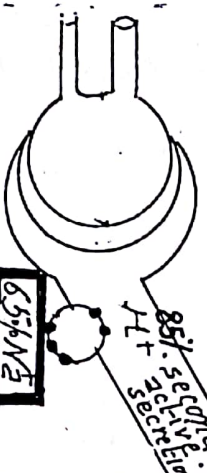
Na^+ accounts for > 90% of osmotically active solutes in ECF
 Na^+ excret. = Fil. - reab. = intake = 1-400 mEq/day

Proximal tubules

Basolab b: Na^+-K^+ pump
 Gradient - Time transport

Luminal b: Na^+-H^+ counter b

1 H^+ secretion : 1 HCO_3^- reab



Results 96

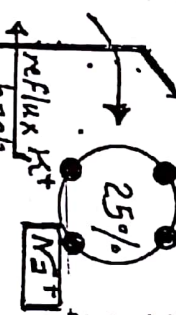
2 [100% Glucose or 100% AA^-]
 or
 2 [65% K^+ or 65% Ca^{++}]

2 [85% HCO_3^-]
 2 [85% H^+]

Cotransport second active reab
 Paracellular 50% DIFF.

Distal tubules

1st part Late part

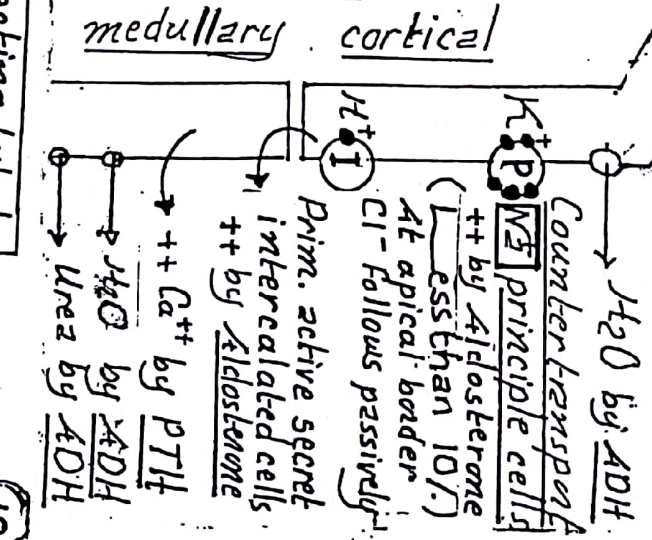


back resulting in paracell. 1 Na^+ 1 K^+ 2 Cl^-
 1 Na^+ 1 K^+ 2 Cl^-
 2 Na^+ 1 K^+ 2 Cl^-

Defect in $\text{Na}^+, \text{K}^+, 2\text{Cl}^-$ cotrans. at luminal b. Result: salt wasting, hypovolemia, hypotension

10% H^+ reab
 10% HCO_3^- 10%
 PASSIVE

Aldosterone, ADH & PTH



Collecting tubules

Regulation of Na^+ excretion 1 - 400 mEq/day

[1] Glomerulo-tubular balance:

Defin ++ GFR $\longrightarrow$ ++ tubular reabsorp. of solute & H_2O

Site PCT main site & Loop of Henle

Mechanism Intrinsic mechanism (independent of hormones)

Prominent for Na^+ Tubules reab constant %

Importance Prevents Na^+ overload of DCT & in turn, Na^+ & H_2O loss

[2] Rate of tubular flow

Slow rate of flow $\longrightarrow$ -- GFR $\longrightarrow$ ++ Na^+ reabsorp.

[3] ABP Pressure naturesis Pressure diuresis

++ ABP $\longrightarrow$ ++ Na^+ & H_2O excretion

Mechanism:

a -- Angiotensin II $\longrightarrow$ -- aldosterone

b Backleak of Na^+ in lumen (++ HP of peritubular capillaries, -- HP of interstitial fluid)

[4] Hormones

a Mineralocorticoids

++ Na^+ reab. via P cell (refer to endo)

b Glucocorticoids

++ Na^+ reab (weak mineralocorticoid)

c Angiotensin II

++ Na^+ reab (most powerful, direct PCT via aldost VC of eFF)

d ANP

++ NaCl & H_2O excretion via

• ++ GFR: Relaxation of mesangial cells VD of eFF VC of eFF.

• -- Renin

• Direct on collecting t $\longrightarrow$ -- Na^+ reab. via Na^+ channel -- Na^+ -K ATPase

++ Na^+ reabsorption

-- Na^+ reab. (++ PGE_2)

-- Na^+ reab. as ANP

e Estrogens

f Endothelin

g PGE_2

[5] Activation of sympathetic nervous system

$\longrightarrow$ ++ Na^+ reabsorption i.e. ++ Na^+ excretion via

a -- GFR (VC of afferent arterioles).

b ++ Angiotensin II (++ Renin).

c Direct action on PCT & Thick ascending loop of Henle

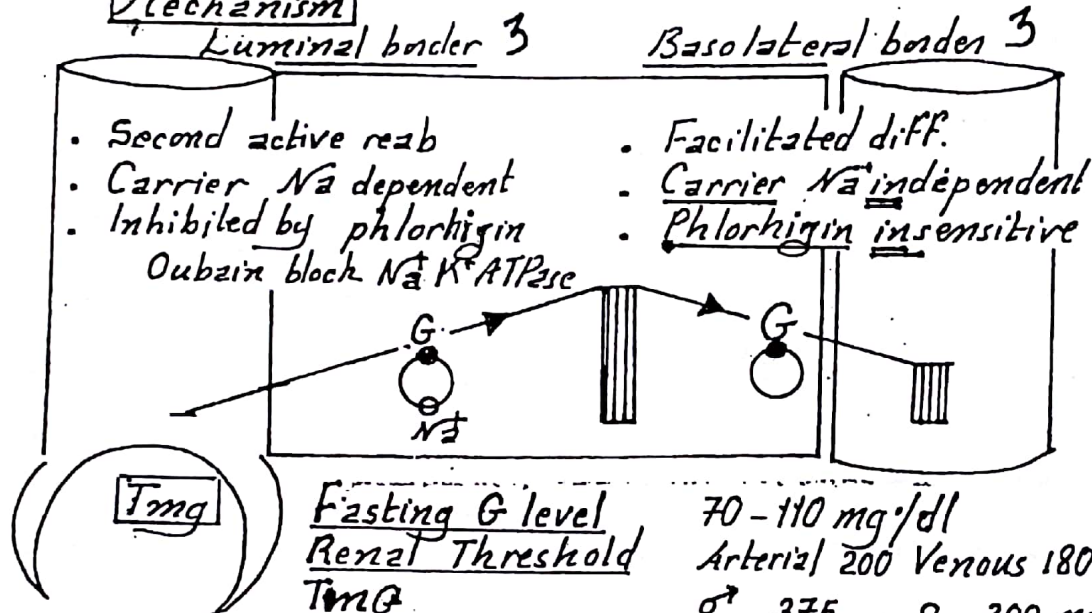
[6] Diuretics

++ Na^+ excretion (see later) (11)

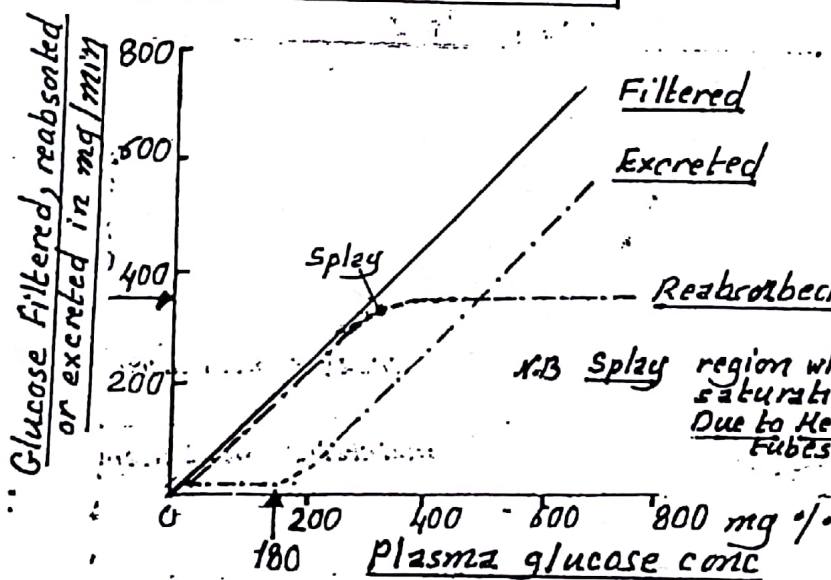
Glucose reabsorption

- Completely reabsorbed only few mg in urine/24 H
- Early portion of PCT
- Secondary active reab. (cotransport with Na^+)

Mechanism



Glucose titration curve



Fasting bl. glucose mg/dl		
< 200	200-300	> 300
+	++	+++
No	Some	All above T _{mg} excreted
All	gradual ++	max no ++

Glycosuria

- Diabetes mellitus ++ Fasting glucose level
- Renal glycosuria -- renal threshold.

Congenital defect in G transport system T_{mg} is also decreased

Result osmotic diuresis & loss of Na^+ & K^+ in urine

Glucose titration curve and T_m

The curve shows relation between plasma glucose concentration and filtration load, reabsorption & excretion rate of glucose. Plasma glucose conc. is increased by infusion of glucose.

Curve is best understood by :

Study of each relation (3) separately then studying all relations together

- Filtration load = $GFR \times [P] \text{ glucose}$

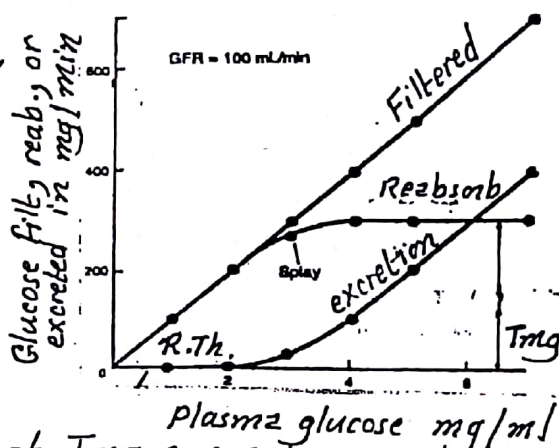
It ++ linearly with ++ plasma.

- Reabsorption ++ gradually to renal threshold, then bend at

splay, then reaches its maximum at T_m & remains so.

Explanation: Gradual saturation of glucose carriers in different nephrons. At T_m all glucose carriers are saturated.

- Excretion Starts at renal threshold, then ++ slightly as some glucose is not excreted (reabsorbed), then ++ markedly & linearly paralleling that of filtration at T_m and above this plasma level.



	up to R threshold	200 to 300 mg dl	Above T_m
<u>Filtered load</u>	+	++	+++
<u>Reabsorption</u>	++ lin. or to Filt	Splay (bend)	no further increase
<u>Excretion</u>	no excretion	+	++ linear to Filt

Excretion of H_2O

500 ml urine	1400 mOsm/L
	1200
23300 ml urine	100 mOsm/L

H_2O reabsorption is a passive process

(A) Obligatory H_2O reabsorption

- Not controlled by ADH
- It includes :
 - 1 Proximal tubules 65%
 - 2 Loops of Henle 15%
 - 3 1st part of DCT 5%
 - 4 Late DCT & collecting tubules 2%
- No change in T. fluid osmolality 87%

(B) Facultative H_2O reabsorption

- Controlled by ADH
- In late DCT & collecting tubules 13%
- It changes the urine concentration.

It depends on 2 factors :

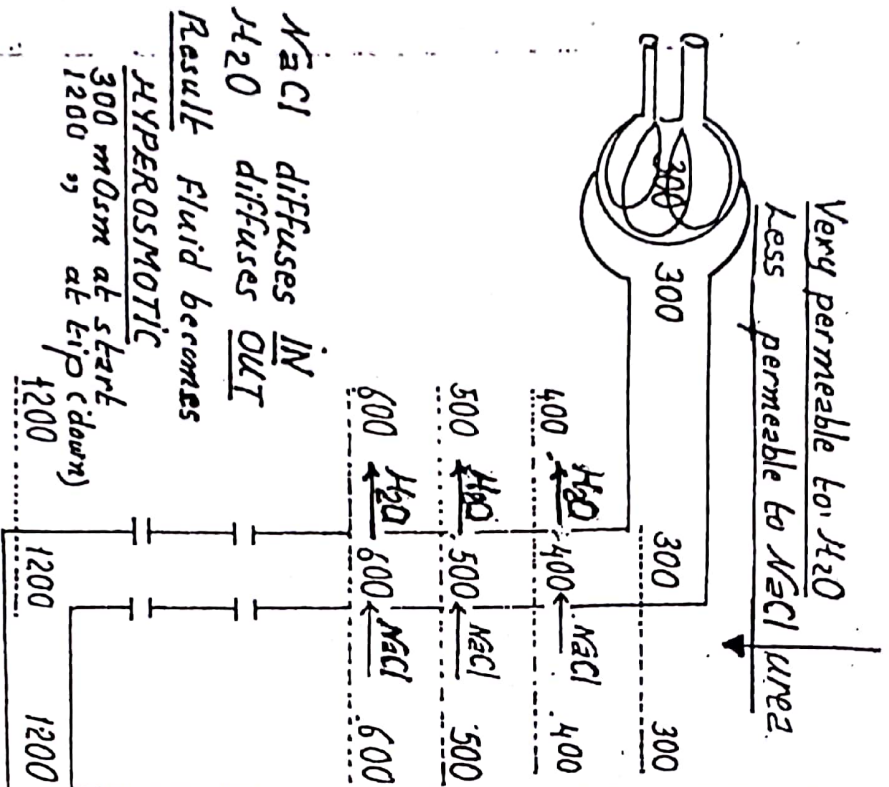
- (1) ADH : ++ permeability to H_2O
via cAMP & V_2 receptors.
- (2) Hyperosmotic gradient of interstitial fluid:
 - superficial layers of medulla : 300 mOsm.
 - deep layers of medulla : 1200 - 1400 mOsm

It is caused by:

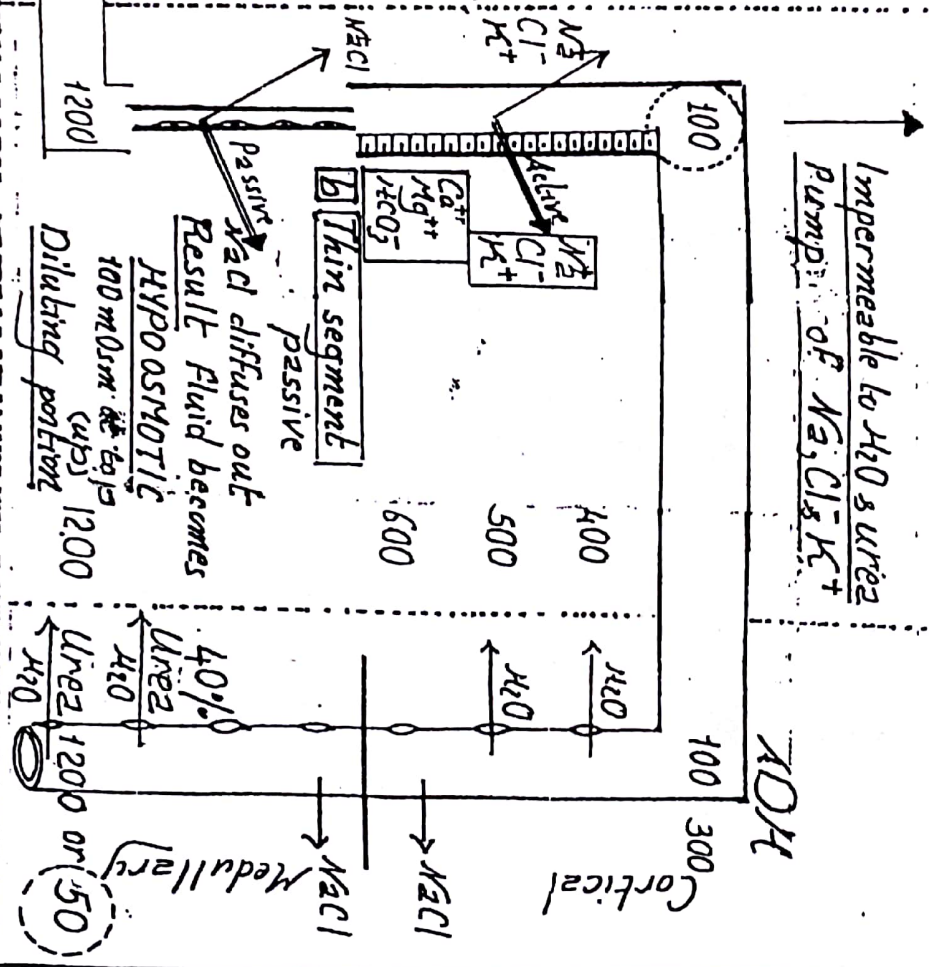
- creates a Loop of Henle creates medullary hyperosmolarity
 maintains b Vasa recta maintains medullary
c Diffusion of urea from the medullary collecting duct to medullary interstitium
d Sluggish medullary flow 1-2%

Loop of Henle counter current multiplier Discuss 1a, b then 2 then 3

2 Descending limb



1 Ascending limb
a Thick segment



3 Interstitial fluid equilibrates osmotically
with descending limb being permeable to H2O

Result. HYPERTONIC gradient from 300 to 1200 mOsm

Vasa recta

Counter current exchanger

Capillaries supplying renal medulla
1 - 2% of RBF

Descending limb

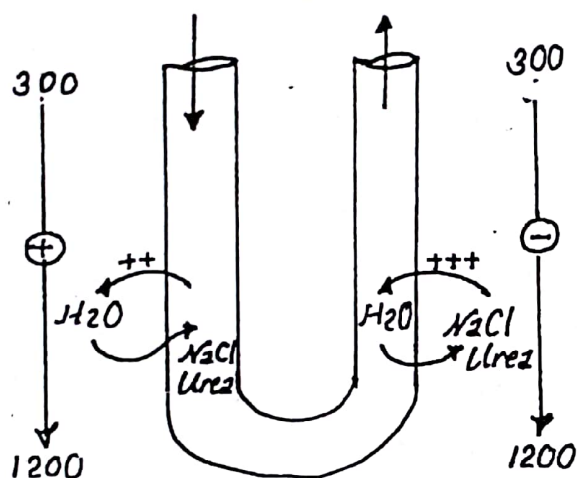
- NaCl & urea diffuse IN
- H_2O diffuses OUT of bl

Result at tip osmolality
1200 mOsm.

Ascending limb

- NaCl & urea diffuse OUT
- H_2O diffuses IN blood

Result opposes & prevents
changes produced by
descending limb



Function

Maintains hyperosmotic gradient via

- 1 Trapping solutes in medulla
 NaCl 60% Urea 40%
- 2 Removal of reabsorbed H_2O
to general circulation

Mechanism of urine conc

In dehydration

- ++ OP of blood
- ++ ADH secretion
- ++ Permeability of distal collecting t
- ++ H_2O reabsorp. Facultative
- ++ Conc. of urine

Maximal 1200 to
1400 mOsmol

i.e. > 4 times that of
plasma

Plasma (300/290) mOsm

Mech. of urine dilution

In overhydration

- OP of blood
- ADH secretion
- Permeability
- H_2O reabsorption
- Conc of urine

Minimal 50 mOsmol

i.e. $\frac{1}{8}$ the plasma

As solutes reabsorption is
strong and active.

(15)

Renal mechanism for excreting diluted urine

Solute are reabsorbed to a greater extent in

- 1 Diluting segment 100 mOsm.
- 2 Distal and collecting T. 50 mOsm.

Role of ADH

++ permeability to H_2O
via insertion of aquaporin 2 H_2O channels into the
Luminal border of principal cells of

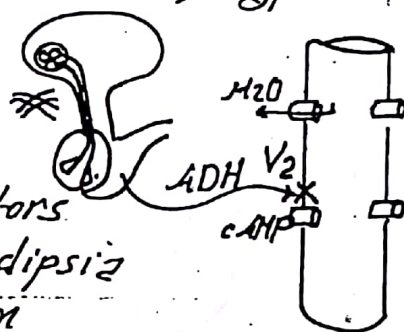
- a late distal & cortical collecting T: 8% of H_2O → fluid isoosmotic
- b Inner medullary collecting tubules: 4.7% of H_2O → „ hyperosmotic

Disorders of urinary concentration

Diabetes insipidus DI

Types: 1 Central DI -- ADH
2 Nephrogenic DI -- V_2 receptors

Effects Polyuria with low sp.gr Polydipsia
If no thirst → fatal dehydration



Diuresis and diuretics

	1 H_2O diuresis	2 Osmotic diuresis
Cause	++ H_2O intake	++ unabsorbable solute
Solute excretion	not ++	++
ADH secretion	inhibited	normal or ++
-- H_2O reab	Facultative	Obligatory & facultative
Maximal urine flow	16 ml/min	Large urine volume
Urine osmolarity	hypotonic	Isotonic or hypotonic

3 Pressure diuresis

4 Diuretic drugs 1, 2, 3

1 Loop diuretic: Lasix (furosemide) inhibits $Na^+-K^+-2Cl^-$ cotransporter

2 Ethanol (alcoholics) -- ADH

3 Caffeine ++ GFR ++ Na^+ reab

4 Antagonists of V_2 receptor

5 Aldosterone inhibitors e.g aldactone

6 Carbonic anhydrase inhibitor e.g diamox -- H^+ secretion
→ Na^+, K^+, H_2O loss

(16)

Tubular handling of K^+

Potassium excretion is determined by the 3 renal processes

1 K^+ filtration. 756 mEq/day (180 L $\times$ 4.5)

2 K^+ reabsorption

a PCT

b Thick ascending

c Collecting T

65%

25% $Na^+, K^+, 2Cl^-$

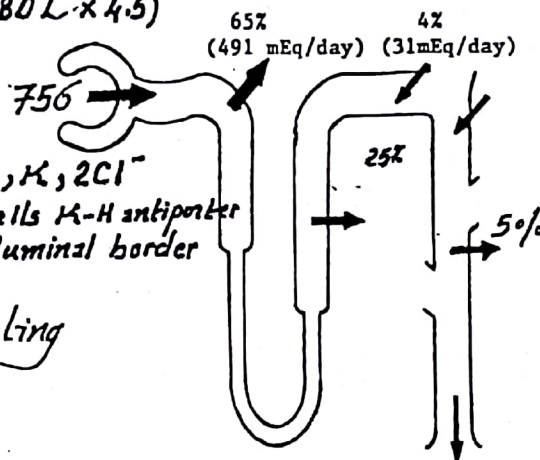
5% I cells H^+ antiporter at luminal border

3 K^+ secretion

Late distal & cortical collecting

P cell

aldosterone



Basolat. border

Luminal border

Na^+-K^+ pump

Diffusion (electrochem. gradient)

The regulation of K^+ secretion

K^+ secretion is increased by :-

1 ++ plasma K^+ conc. i.e ++ dietary K^+

2 ++ Flow rate in distal tubule e.g. diuretics

3 Metabolic alkalosis Mechanism ++ tubular cell conc. of K^+ viz

1 Stim Na^+-K^+ ATPase 2 -- K^+ efflux & H^+ uptake by cortical collect. cells

4 Aldosterone

Tubular handling of urea

1 PCT : 40 % back diffusion

2 Thick ascending, DCT & collecting T : impermeable to urea

H_2O reabsorption $\rightarrow$ ++ urea concentration

3 Medullary part of collecting tubules Urea diffuses 40%-60% to medullary interstitium $\rightarrow$ hyperosmolarity

Urea excretion is increased by:

1 ++ plasma urea

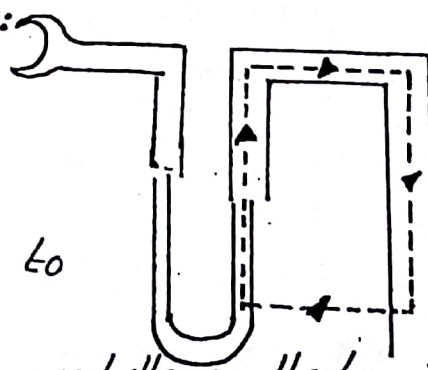
2 ++ GFR

Urea cycle

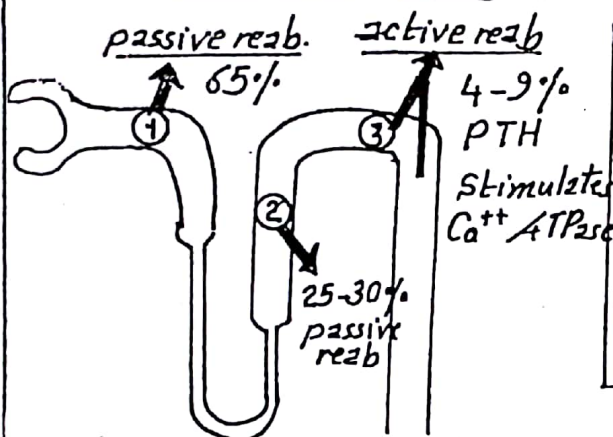
Medullary collecting tubule to

Medullary interstitium to

thin loop of Henle back to medullary collecting T



Ca⁺⁺ handling by renal tubules



++ Ca reabsorp.	-- Ca^{++} reabsorp
++ PTH	-- PTH
++ 1,25(OH) ₂ CC	CT
Metabolic acidosis	Metabolic alkalosis
++ PO_4 plasma conc	-- PO_4 plasma conc
-- ECF volume or -- ABP	

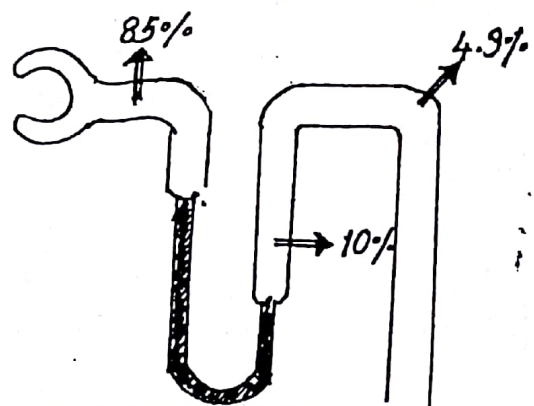
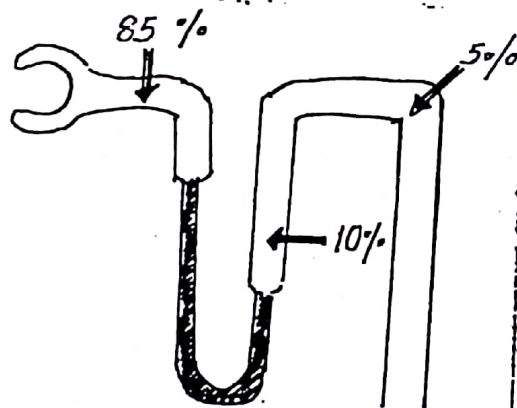
Mechanism of 1 & 2 ++ Na^+ & H_2O reab. $\rightarrow$ ++ Ca conc in lumen $\rightarrow$ ++ Ca^{++} reabsorption

Secretion of hydrogen and

For each H^+ ion secreted H^+ ions are secreted in all except descending & ascending thin limbs of Loop of Henle

Reabsorption of HCO_3^-

One HCO_3^- ion is reabsorbed. Tubules are poorly permeable to HCO_3^- . Reab. HCO_3^- is formed by tubular cells from $\text{CO}_2 + \text{H}_2\text{O} \xrightarrow{\text{CA}} \text{H}_2\text{CO}_3 \rightarrow \text{HCO}_3^- + \text{H}^+$

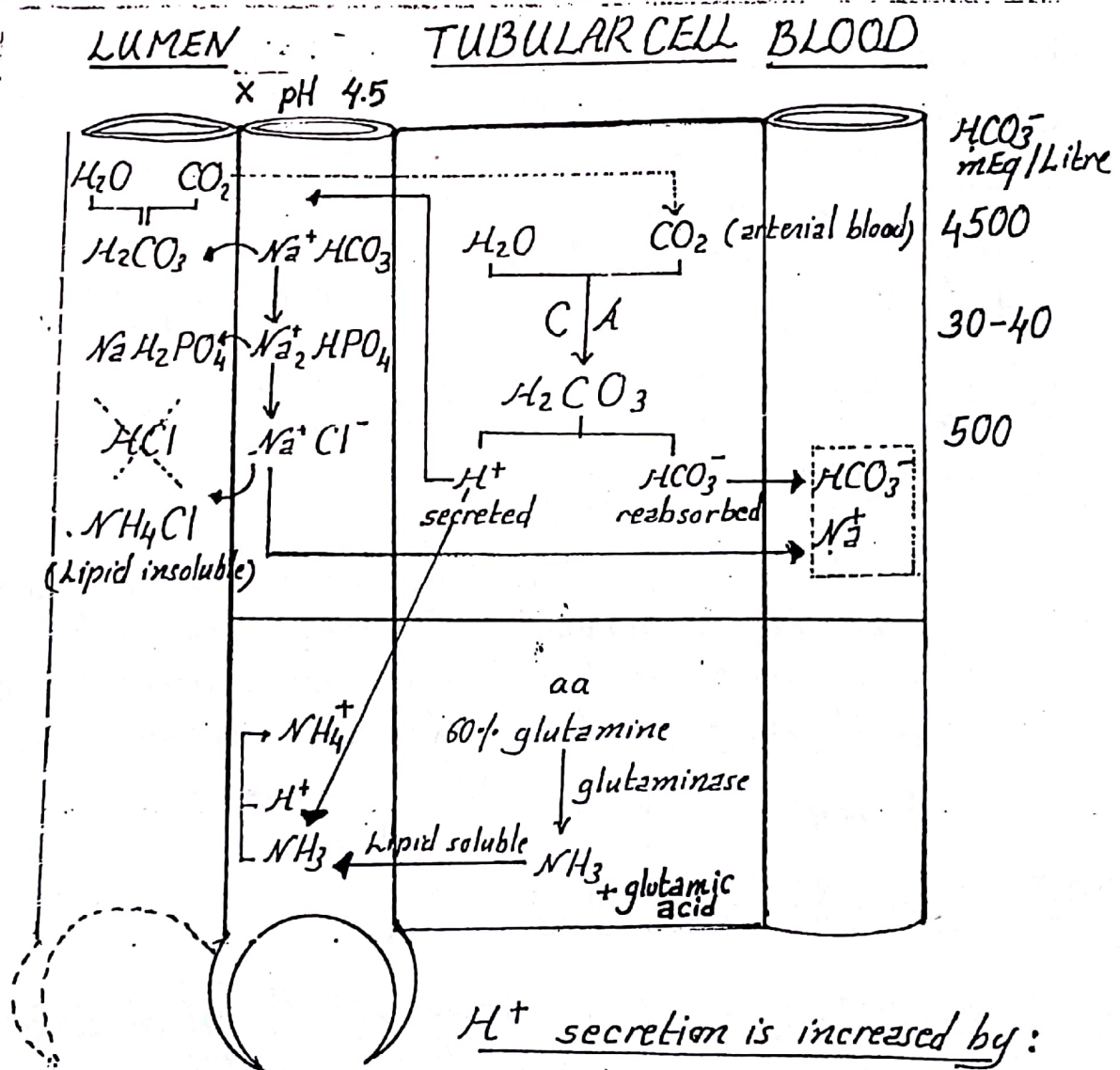


	Secondary active transport	Primary active transport
<u>Site</u>	PCT loop of Henle (thick) 1st part of DCT	Late DCT and collecting tubules
<u>%</u>	95%	5%
<u>Mechanism</u>	Na^+ dependent Antiport carrier at luminal border	Na^+ independent H^+ ATPase pump at luminal border
<u>Control</u>	Not stim by aldosterone	Stimulated by aldosterone

Fate of H^+ secreted:

Three important reactions remove Free H^+

- ① In PCT pH of tubular fluid is very little changed.
Buffering by $NaHCO_3 \rightarrow H_2CO_3 \xrightarrow{CA} H_2O + CO_2$ diffuses to cell.
- ② In DCT & collecting tubules pH never falls below 4.5 (H^+ secretion stops)
Buffering by phosphate buffer $\rightarrow$ titratable acidity
Buffering by $NH_3 + H^+ \rightarrow NH_4 + Cl^- \rightarrow NH_4Cl$
In all 3 buffers Na^+ is reab. with $HCO_3^- \rightarrow ++ NaHCO_3$ in bk (alkali reserve) formed in tubular cells



H^+ secretion is increased by:

- 1 Aldosterone
- 2 ++ intracellular CO_2 ⑬
- 3 -- intracellular K^+

Plasma clearance

- Definition Volume of plasma cleared completely from a substance excreted in urine per minute.
- Calculation

$$C \times P = V \times U$$

$$C \text{ (vol. cleared)} = \frac{V \times U}{P}$$

$V = \text{Vol of urine/min}$ $U = \text{Urine conc.}$ $P = \text{Plasma conc.}$

- Importance

- 1 Study of tubular handling of different solutes (p.21)

- 2 Measurement of GFR refer to inulin clearance

- 3] Measurement of a) $ERPF = PAH$ clearance.
total renal plasma flow b) $TRPF$ Extraction ratio 90%.

Characters of PTH :

- Completely secreted c)
- through a single circ.
- Freely filtered

ie only 90% of TRPF goes to nephron
 $\text{TRBF} \times 0.9 = \text{RPF}$ From hematocrite value

$$TRBF = \frac{TRBF}{1 - HV}$$

4. Calculation of Filtration fraction $\frac{GFR}{RPF} = 0.2$

- 5) Free water clearance
= H_2O free of solute

It tests power of kidney to conc. or dilute urine
Free H_2O is generated by diluting segment

- If ADH is low: free H_2O clearance is +ve

- If ADH is high: Free H_2O clearance is -ve

$$C_{H_2O} = V - \frac{V \times U_{osm}}{P_{osm}}$$

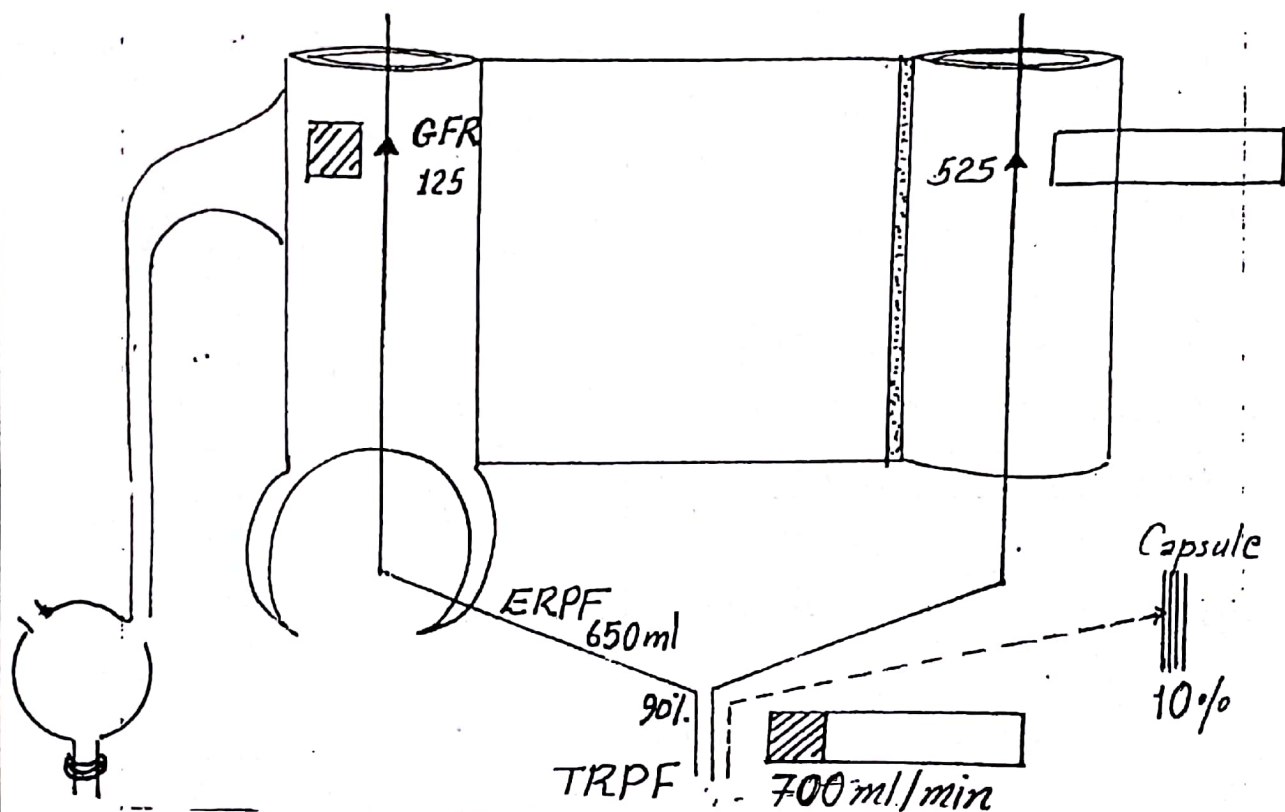
6 Kidney function tests

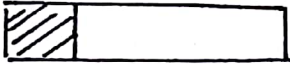
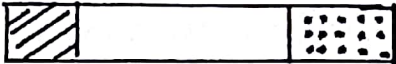
- Disadvantages It gives net effect not the detail.
e.g. K^+ clearance less than 125 ml/min

so • net effect: partial reabsorption

- Details: K^+ is completely reab. in PCT then secreted in DCT

Plasma clearance



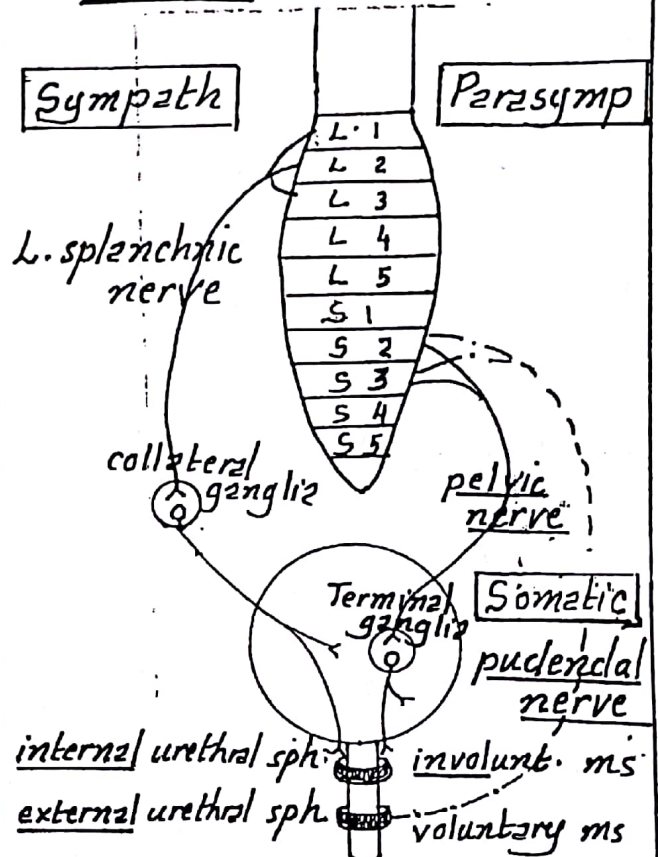
	Clearance ml/min	Renal mechanism	e.g
	(125)	neither reab. nor secreted	Inulin
	Less than 125	partially reab	K ⁺ Urea
	0	completely reab	Glucose
	More than 125	partially secreted	Creatinine
	(650)	completely secreted	PAH diodrast
	More than 650	Formed & secreted	NH ₃ (21)

Micturition = Filling + Micturition reflex

Anatomy

- 1 Body: detrusor ms
Functional syncytium
Cont. $\rightarrow$ $\uparrow$ p to 40-60 mmHg
- 2 Neck Internal urethral sphincter
Extension of detrusor ms
 - It keeps post. urethra empty.
 - Prevents reflux of semen.
- 3 External urethral sphincter
Voluntary muscle
Ureter passes obliquely few cms in bladder wall
 So, tone of detrusor ms prevents reflux of urine in ureter.

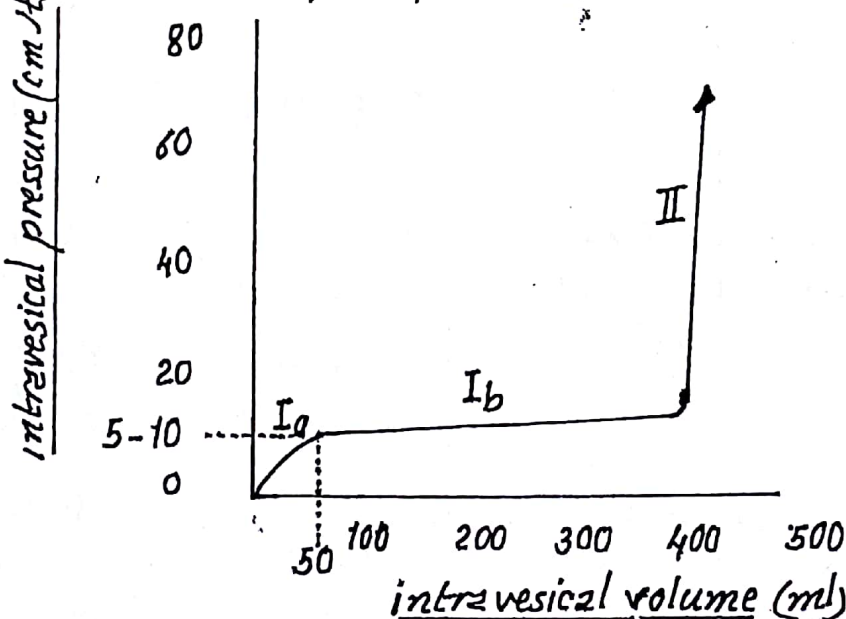
Innervation of bladder sphincters
Efferent



Bladder Filling

Cystometrogram

Intravesical p is plotted against urine volume.



1st urge 150 ml

Marked sensation of fullness 400 ml

I_b is due to plasticity
Laplace law

$$\pm p = \frac{2T}{r}$$

Afferents

Parasympathetic n.s.

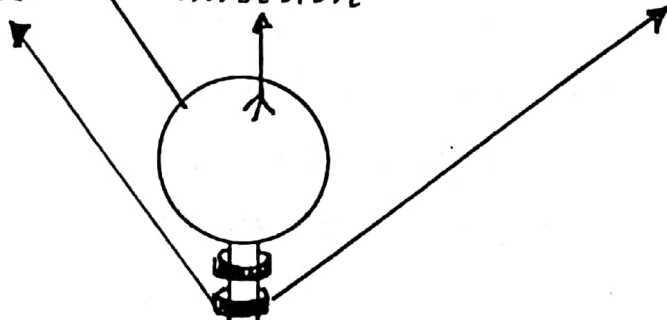
- 1 detect degree of bladder stretch
- 2 of post. urethra: initiates reflex blad. emptying

Sympathetic n.s.

- 1 Sensation of fullness
- 2 Pain due to overstretch or infection

Somatic n.s.

- From stretch receptors of post. urethra: sensation of urine flow to urethra



Micturition reflex

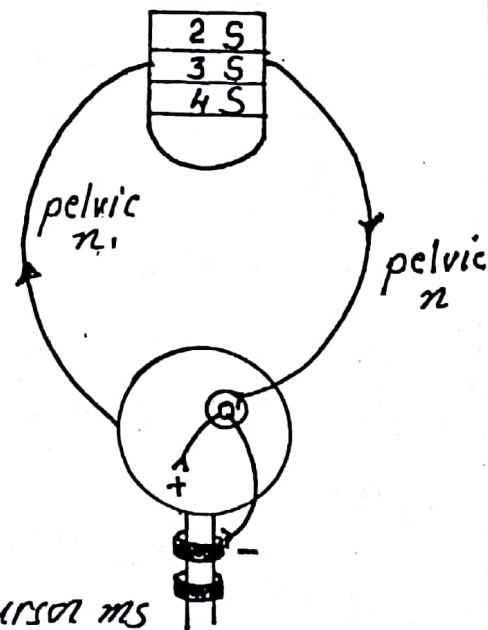
Occurs in infant

adult Complete TS of sp. cd above sacral region

Initiated at 300 - 400 ml urine vol

Reflex

- Stimulus bladder distension
- Receptors Stretch receptors in bladder wall post. urethra
- Afferent Pelvic parasymp nerve
- Centre 2, 3 & 4 Sacral
- Efferent Pelvic parasymp nerve
- Response - Contraction of wall detrusor ms
- Relaxation of internal sphincter



N.B Micturition is self regenerative i.e contraction activates stretch receptors (bladder & post urethra) → further ++ in bladder cont
Once micturition reflex is powerful → another reflex viz pudendal nerve to relax external urethral sphincter

Higher control of micturition reflex

Cortical micturition centre : Superior frontal gyrus

Facilitatory centre : Pons Post. hypoth.

Inhibitory centre : Midbrain

When it is time to urinate, cortical centres

- Facilitate sacral centre to initiate mict. reflex.

- Inhibit ext. urethral sphincter

Voluntary micturition is initiated by :

a Relaxation of pelvic floor muscles

→ downward tug on detrusor muscle to initiate its contraction.

b Voluntary cont. of abdom. muscles

→ ++ intravesical p → entry of urine in bladder neck

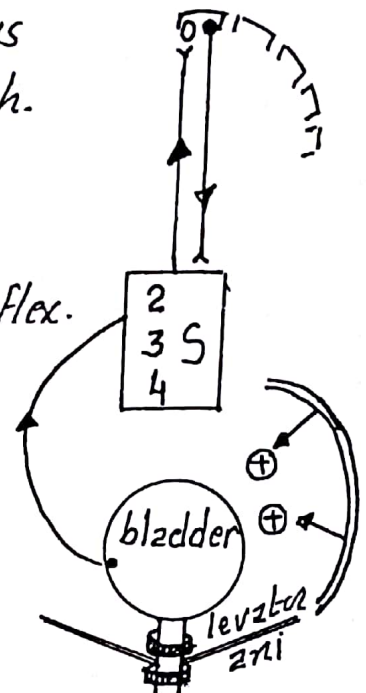
→ stretch of bladder neck → stim. stretch receptors

→ excite micturition reflex

c Relaxation of external urethral sphincter

After micturition & urethra empties by gravity.

or urethra empties by contraction of bulbocavernosus muscle.



Abnormalities of micturition :

Items \ Lesion	Deafferentiation	Denervation	Sp cd damage
<u>Cause</u>	Damage of aff. e.g. Tabes dorsalis	Damage of aff & efferent nerves	T.S. of sp. cd above sacral region
<u>Mict. reflex</u>	Abolished	Abolished	lost then recovered
<u>Volunt. control</u>	Lost	lost	Lost
<u>Bladder</u>	Thin distended hypotonic	Thick shrunken hyperactive	Shock stage: Flaccid Recovery → hypertroph
<u>Urination</u>	Bladder is full & overflows in drops by intrinsic response	Hyperactive bladder expels drops of drop	Shock stage: retention with overflow (24) Recovery stage automatic bladder

Kidney function tests

[1] Blood analysis :

- Blood urea All values ++ in renal insufficiency
20 - 40 mg/dl nonspecific rough test
++ liver disease & ++ protein intake & dehydration
- Plasma creatinine 0.6 - 1.5 mg/dl more accurate.
- Potassium 3.5 - 5 mEq/L
- Inorganic phosphate 2.6 - 4.5 mg/dl
- Serum uric acid ♂ 3.6 - 8.5 ♀ 2.3 - 6.6 mg/dl
- Blood pH arterial 7.4 venous 7.35

[2] Urine analysis :

- a Volume 500 - 1500 ml / day
- Polyuria: DM, DI & diuretics Oliguria: Dehydration acute renal failure
- Anuria: Acute vascular thrombosis & total urinary obstruction.
- b Sp. gr 1010 - 1020 Low: DI High: DM
- Low Fixed at 1010 = plasma in chronic renal failure
- c H₂O diuresis test: evacuate bladder then drink 1.5 L & collect urine for 4 hours Normal results 800 ml sp. gr < 1003 OP below 80 mOsm
- d H₂O conc. test: evacuate bladder & stop drinking for 12 hours Normal results -- urine vol sp. gr 1025-1030 OP of urine > 900 mOsm.

[3] Tests depending on blood and urine analysis Plasma clearance

- a Creatinine clearance measures GFR
- b PAH clearance measures ERPF
- c Urea clearance measures Renal tubular function

Vol of urine 2 ml or more/min	Urine volume less than 2 ml/min
Maximal urea clearance	Standard urea clearance
$C_m = \frac{U \times V}{P}$	$C_s = \frac{U \times \sqrt{V}}{P}$
Normally 70 ml/min.	Normally 54 ml/min. (25)
Urea clearance 5% below normal indicates renal impairment	

It is an early test, specific test & quantitative test.

[4] Imaging Techniques

- Plain x ray: shows opaque calculi & calcifications
- Intravenous urography IV iodine e.g diodrast, then series of radiographs. to show nonopaque calculi, stricture, dilated pelvis and nonfunctioning kidney.
- Ultrasonography: shows renal size, position, tumor, cysts or dilatation of collecting system in obstruction.
- Computed tomography CT shows tumor or cysts.

Treatment of chronic renal failure

- Dialysis treatment: Diffusion of molecules viz a semipermeable mem.
 - Kidney machine (hemodialysis) course 6 hours 2-3 times/wk remove urea 50-250g/6H & toxins and add HCO_3^- in acidosis
 - Continuous ambulatory peritoneal dialysis CAPD
 Fluid is collected from peritoneal cavity 4 to 8 hours later.
 Dialysis fluid should contain less K^+ than plasma, be buffered, free of urea and has higher OP than normal plasma $\rightarrow$ -- ABF
- Kidney transplants should correct:
 GFR to 120-150 ml, abnormal Ca homeostasis & anemia.

Acid-base balance

- Acid base state = Acid base state of ECF

Acid	Base
Molecule produces H^+ i.e proton donor	Molecule combines with H^+ i.e H^+ acceptor
Strong e.g 100% dissociation	Strong e.g NaOH 100% dissociat.
Weak e.g H_2CO_3 1% "	Weak e.g NH_4OH 1% "
Free H^+ conc. in ECF is very low 0.00004 mmol/L 40 mmol/L	

- Determined by measuring in ARTERIAL blood 2 out of 3
 - 1 $[H^+]$ 35 - 45 nanomol/L (pH 7.35 - 7.45)
 - 2 PCO_2 35 - 45 mmHg
 - 3 $[HCO_3^-]$ 22 - 26 mEq/L
- Protein mediated processes depend on pH
i.e. enzymes, transport molecules & contractile molecules
- Sources of H^+
 - 1 Ingested: Food
 - 2 Metabolism
 - a CHO generates 12,000 - 20,000 mmol/day H_2CO_3 (volatile acids)
 - b Protein & lipid generate 60 mmol/day H_2SO_4 , H_3PO_4 (Fixed acids)
 - c Lactic acids in severe exercise due to inadequate O_2
 - d ketoacids in DM

Amount of H^+ in ECF is very small compared to amount of H^+ produced/D
 $pH = -\log_{10} \text{ of } H^+ \text{ conc} = -\log_{10} 0.00004 = 7.4$ alkaline
 Death occurs if pH falls below 6.8 or rises above 8.0.

- Regulation of acid base balance:
 - 1 Chemical buffers minimise change in pH (fraction of a sec)
 - 2 Respiratory system removes H^+ of volatile acids (minutes)
 - 3 Kidney (most important) removes H^+ of fixed acids (hours to days)
restores ECF buffers

Chemical buffers

7 points

- Substances which minimise changes of pH.
- Act within Fraction of a second
- Molecules that combine with or release H^+
- Buffer system = weak acid + salt of its conjugate base
- Henderson Hasselbach equation:

$$pH = pK + \log_{10} \frac{[Salts]}{[Acids]}$$

- Effectiveness of any buffer system depends on :

- 1 Amount of buffer pair
- 2 pK Most effective when $pH = pK$

- Three major buffers :

1 Bicarbonate

Amount 24 mmol/L Disadvantage
pK 6.1

2 Phosphate

Amount 1 mmol/litre
Except in ECF
& tubular fluid

2 components can be Advantage pK 6.8
regulated < lung PCO_2
Kidney HCO_3^-

3 Prtn.

a Plasma prtns

b Hb 6 times buffering power of plasma prtn.
Large amount 700 g in adult 38 histidine/molecule
Deoxy Hb is better buffer than oxy Hb
It buffers CO_2 (Cl⁻ shift phenomenon)
In renal failure, -- Hb leads to more acidosis

c Intracellular prtns & organic phosphate.

Advantages: Backup extracellular buffer
Most plentiful.

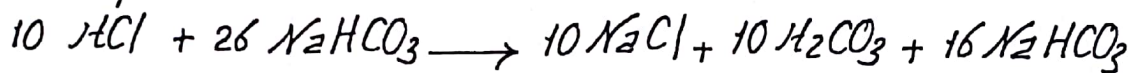
Disadvantages: Slow (hours); cell mem has permeability to H^+
 H^+ is exchanged with K^+ & Ca^{++} → depletes
cells of K^+ and bones of Ca^{++}

- 7 Isohydric principle: The buffer systems buffer each other
by shifting of H^+ ions from one buffer to others

Respiratory control

- Controls blood PCO_2
- Mechanisms via peripheral chemoreceptors
e.g. $++ PCO_2 \rightarrow ++ [H^+] \rightarrow \text{stim. of periph. chem} \rightarrow -- PCO_2$
- Effectiveness of respiratory control.
 - 1 Returns $[H^+]$ $\frac{2}{3}$ the way back to normal.
within 1-12 minutes
 - 2 1-2 times buffering power of chemical buffers.
 - 3 Limited ability PCO_2 changes have $\neq$ effect on resp.

Example



i.e. H_2CO_3 $++$ 10 mmol/L $NaHCO_3$ $--$ 10 mmol/L

According to Henderson-Hasselbalch equation

$$pH = 6.1 + \log \frac{26-10}{1.3+10} = 6.1 + \log \frac{16}{11.3} = \textcircled{6.25}$$

incompatible with life

However, hypervent. eliminates 10 mmol/L of carbonic acid.

$$\text{So, } pH = 6.1 + \log \frac{26-10}{1.3} = 6.1 + \log \frac{16}{1.3} = \textcircled{7.3}$$

compatible with life

Renal control

- It is the most powerful.
- Returns pH back to normal within 12-14 hours.
- Mechanism discussed before.

Acid-Base disturbance table page 30

pH depends on $\frac{CO_2 \text{ in chemical}}{CO_2 \text{ in physical}}$ i.e. $\frac{[HCO_3^-]}{PCO_2}$

So, disturbance is caused by changes either in $[HCO_3^-]$ or PCO_2

It is corrected by change in the second system

$\rightarrow$ ratio return to normal but HCO_3^- & PCO_2 are $\oplus\oplus$ or $\ominus\ominus$ (29)

Respiratory control

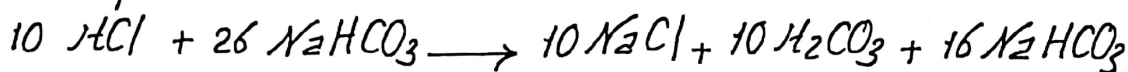
- Controls blood PCO_2
- Mechanisms via peripheral chemoreceptors
e.g. $++ PCO_2 \rightarrow ++ [H^+] \rightarrow \text{stim. of periph. chem} \rightarrow -- PCO_2$
- Effectiveness of respiratory control.

1 Returns $[H^+]$ $\frac{2}{3}$ the way back to normal.
within 1-12 minutes

2 1-2 times buffering power of chemical buffers.

3 Limited ability PCO_2 changes have $\neq$ effect on resp.

Example



i.e. H_2CO_3 $++$ 10 mmol/L $NaHCO_3$ $--$ 10 mmol/L

According to Henderson-Hasselbalch equation:

$$pH = 6.1 + \log \frac{26 - 10}{1.3 + 10} = 6.1 + \log \frac{16}{11.3} = 6.25$$

incompatible with life

However, hypervent. eliminates 10 mmol/L of carbonic acid.

$$\text{So, } pH = 6.1 + \log \frac{26 - 10}{1.3} = 6.1 + \log \frac{16}{1.3} = 7.3$$

compatible with life

Renal control

- It is the most powerful.
- Returns pH back to normal within 12-14 hours.
- Mechanism discussed before.

Acid-Base disturbance table page 30

pH depends on $\frac{CO_2 \text{ in chemical}}{CO_2 \text{ in physical}}$ i.e. $\frac{[HCO_3^-]}{PCO_2}$

So, disturbance is caused by changes either in $[HCO_3^-]$ or PCO_2

It is corrected by change in the second system

$\rightarrow$ ratio return to normal but HCO_3^- & PCO_2 are $++$ or $--$

Acidosis			Alkalosis		
	Respiratory	Metabolic	Respiratory	Metabolic	
$\downarrow$ pH <u>Causes</u>	$\uparrow$ $\frac{[HCO_3^-]}{PCO_2}$ Hypovent 1 Resp. centre -- 2 Resp muscles paralysis 3 Lung diseases Obstr. or restrictive	$\downarrow$ $\frac{[HCO_3^-]}{PCO_2}$ 1 DM 2 Shock 3 Loss of intest content 4 Renal failure	$\uparrow$ pH <u>Causes</u>	$\downarrow$ $\frac{[HCO_3^-]}{PCO_2}$ Hypervent 1 High altitude 2 Early in exercise 3 Fever 4 Meningitis 5 Psychological anxiety 5 Cushing's	$\uparrow$ $\frac{[HCO_3^-]}{PCO_2}$ 1 Persistent vomiting 2 Diuretics 3 ++ intake of alkali 4 ++ fruits & vegetables 5 Cushing's
<u>Compensation</u> $\uparrow \downarrow$ pH	1 Chemical buffers 2 $\uparrow$ $\frac{[HCO_3^-]}{PCO_2}$ Renal $\uparrow \downarrow$ $[HCO_3^-]$ 3 $\uparrow$ PCO_2 Resp $\downarrow$ PCO_2 Hypervent	<u>Compensation</u> $\uparrow \downarrow$ pH	1 Chemical buffers 2 $\downarrow$ $\frac{[HCO_3^-]}{PCO_2}$ Renal $\uparrow \downarrow$ $[HCO_3^-]$ 3 $\downarrow$ PCO_2 Resp $\uparrow$ PCO_2 Hypoventilation	<u>Compensation</u> $\uparrow \downarrow$ pH	1 Chemical buffers 2 $\downarrow$ $\frac{[HCO_3^-]}{PCO_2}$ Renal $\uparrow \downarrow$ $[HCO_3^-]$ 3 $\downarrow$ PCO_2 Resp $\uparrow$ PCO_2 Hypoventilation
<u>Laboratory diagnosis</u> 22-28 mEq/L 35-45 mmHg	pH meter Alkali reserve Arterial PCO_2 $\boxed{+}$ $\boxed{-}$	<u>Laboratory diagnosis</u> Arterial blood $\boxed{-}$ $\boxed{+}$	pH meter Alkali reserve Arterial PCO_2 $\boxed{-}$ $\boxed{+}$		
<u>Clinically</u> CNS Resp.	Drowsy & finally comatose Hypovent.	<u>Clinically</u> CNS Respiration	Tetany & convulsion Hypervent.		

N.B. Resp. compensation is less powerful in metabolic alkalosis than in metabolic acidosis

Kidney & Body Fluids

The kidneys have major homeostatic functions:

- 1) Regulation of water and electrolyte balance.
- 2) Regulation of acid-base balance by:
 - a- Excretion of acids produced from metabolism of proteins.
 - b- Regulation of the buffer stores in the body.
 - c- Formation of ammonia.
- 3) Regulation of ABP:
 - a- Short term: renin-angiotensin system.
 - b- Long term: via excretion of variable amount of Na^+ & H_2O to keep plasma volume constant.
- 4) Excretion of metabolic waste products e.g. urea, uric acid, creatinine, metabolites of hormones & bilirubin.
- 5) Excretion of foreign chemicals e.g. drugs, food additives & pesticides.
- 6) **Endocrinal function:** Kidney secretes:
 - a- Erythropoietin 85%, so severe kidney diseases lead to anemia.
 - b- 1,25 dihydroxy cholecalciferol (active vitamin D3).
 - c- Renin.
- 7) **Paracrine function:** Kidney secretes:
 - a- Prostaglandins: PGE_2 & PGI_2 .
 - b- Bradykinin.They play important role in regulation of renal blood flow.
- 8) **Gluconeogenesis** during prolonged fasting.

Physiologic anatomy of the kidney

- **Weight:** each adult kidney weighs 150 gram.
- **Size:** clenched fist < 12 cm length x < 8 cm width.
- The renal mass is divided into 2 major regions:
 - a- An outer cortex: granular and deeper in colour.
 - b- An inner medulla: striated and paler in colour.The medulla is divided into renal pyramids.

Each pyramid tapers to form a renal papilla.

Each papilla projects into the pelvic space via minor calyx.

The minor calyces converge into 2 or 3 major calyces, which converge to form the pelvic of the ureter.

Calyces, renal pelvic & ureter are surrounded by smooth muscles.

Microscopic anatomy:

- Each human kidney contains 1.3 million nephron.

- Nephron is the functional unit of the kidney

Each nephron acts as a separate entity & is composed of:

a) Glomerulus:

A tuft of capillaries which lies within the dilated blind end of renal tubule (Bowman's capsule). These capillaries lie between afferent arteriole and a smaller efferent arteriole.

Glomerulus is a high-pressure capillary bed 60 mmHg.

b) Renal tubule: is divided into:

1) Proximal convoluted tubule: PCT

- 15 mm long that lies in the cortex.

- It is made up of a single layer of cells.

- At the apex: the cells unite by tight junctions & have distinct brush border & many mitochondria.

- At the bases of cells, there are extensions of the extracellular space called lateral intercellular spaces.

2) Loop of Henle:

- U shaped, that dips in the renal medulla.

- It is composed of:

- a- Thin segment i.e. descending limb & lower $\frac{1}{2}$ of ascending limb. It is lined by flat epithelium.

- b- Thick segment i.e. rest of ascending limb. It is lined by cuboidal cells.

3) Distal convoluted tubule: DCT

- 5 mm long that lies in the cortex.

- No distinct brush border but few microvilli.

4) Collecting duct:

- 20mm that passes through cortex & medulla.

- They empty into pelvis at the apexes of pyramids.

- They are lined by 2 types of cells:

Principal cells (P cells)	Intercalated cells (I cells)
1- Predominant cells. 2- Less microvilli, mitochondria & cytoplasmic vesicles. 3- Function Na^+ reabsorption, H_2O reabsorption via ADH.	1- Smaller number. 2- More microvilli, mitochondria & cytoplasmic vesicles. 3- Function: acid secretion, Bicarbonate reabsorption.

- Types of nephrons: 2 types

Items	Cortical nephrons	Juxta medullary Nephrons
- % of total	85%	15 %
- Glomerulus	<u>Outer</u> part of cortex	<u>Inner</u> part of cortex near the medulla.
- Loop of Henle	<u>Short</u> i.e. dips to the junction between inner & outer medulla.	<u>Long</u> i.e. dips deeply into the medullary pyramids.
- Blood supply	Peritubular capillaries.	<u>Vasa recta</u> & peritubular capillaries.
- Special function		<u>Urine concentration.</u>

Juxta glomerular apparatus

- Specialized tubular & vascular cells at area of contact between the distal convoluted tubule and the afferent and efferent arterioles at the vascular pole, where they enter & leave the glomerulus.

- It consists of:

1) Macula densa:

They are modified tubular cells in 1st part of DCT in close proximity to the juxta - glomerular cells.

Macula densa monitor the composition of tubular fluid i.e. functions as chemoreceptors that are stimulated by a decrease of NaCL load in DCT.

2) Juxta glomerular cells	3) Lacis cells
Granular cells. Located in media mainly of afferent arteriole. Secrete renin. Act as baroreceptors stimulated by decreased renal perfusion or by hypovolemia.	Agranular cells. Located between afferent and efferent arterioles. Store renin.

- Function:

Autoregulation of renal blood flow and glomerular filtration during changes in ABP (see later)

Renal blood flow: RBF

- Kidneys receive 20-25 % of COP i.e. 1.2 –1.3 liter /min.

- Renal vascular arrangement:

Each renal artery divides to form the interlobar arteries, arcuate arteries and interlobular arteries → afferent arterioles → glomerular capillaries → efferent arterioles → peritubular capillaries (also vasa recta) → interlobular veins → arcuate veins → interlobular veins → renal veins.

- There are two capillary bed related to each nephron:

Glomerular capillary bed	Peritubular capillary bed
1- Receive blood from <u>afferent</u> artery.	1- Receive blood from <u>efferent</u> artery.
2- <u>High</u> pressure bed <u>60</u> mmHg.	2- <u>Low</u> pressure bed <u>13</u> mmHg.
3- Represents <u>arterial</u> end of capillaries.	3- Represents <u>venous</u> end of capillaries.
4- It allows fluid <u>filtration</u> .	4- It allows fluid <u>reabsorption</u> .

Note:

The pressure in the glomerular capillary is high due to:

- Renal artery is a direct branch of the abdominal aorta.
- Afferent arteriole is a short straight branch of the interlobular arteries.
- Efferent arteriole has higher resistance than the afferent arteriole.

Regional blood flow:

Renal cortex receives most of the renal blood flow to filtrate large volumes of blood through the glomeruli.

Renal medullary blood flow accounts only for 1-2% of the total renal blood flow.

Autoregulation of the renal blood flow

- RBF is kept relatively constant between ABP 90 – 220 mmHg.
- Autoregulation of RBF is present in denervated or isolated kidney i.e. independent of nerves or hormones.

- Mechanism:

It occurs by changing the renal vascular resistance.

1) At high pressure

++ ABP $\longrightarrow$ stretch of afferent arteriole $\longrightarrow$ ++ Ca^{++} influx from extracellular fluid into muscle fiber $\longrightarrow$ direct VC $\longrightarrow$ prevent ++ in RBF.

2) At low pressure:

a- Angiotensin II causes VC of the efferent arteriole thus maintaining the GFR.

b- Tubuloglomerular feedback (discussed later).

- Aim of autoregulation:

It is to maintain constant GFR and to allow precise control of renal excretion of H_2O & solutes with marked changes in ABP.

Innervations of the renal vessels and the renal tubules

Sympathetic stimulation causes:

1- Vasoconstriction with --- the renal blood flow & GFR via alpha receptors during exercise, rising from the supine to the standing position or when ABP ---

2- Renin secretion from juxta glomerular apparatus via Beta₁ receptors.

3- Increased Na^+ reabsorption by renal tubules by direct action of norepinephrine on renal tubular cells α or β receptors or both.

Formation of urine

It involves 3 processes:

1- Glomerular filtration into Bowman's capsule.

2- Tubular reabsorption from tubular lumen to peritubular capillaries.

3- Tubular secretion from peritubular capillaries to tubular lumen.

Excretion refers to what finally comes out in urine.

It represents the sum of the three processes

Urinary excretion rate = filtration rate - reabsorption rate + secretion rate.

Glomerular filtration

Glomerular filtrate

It is a protein free ultra filtrate.

1- Composition:

Plasma minus colloids (plasma proteins).

2- Volume:

Normal glomerular filtration rate: GFR)

- In an average man: 125 ml / minute.
- In women: 10 % less than those of men.
- GFR: 7.5 L / hour or 180 L / day i.e. 60 times plasma volume.

More than 99% of GFR is normal reabsorbed.

Normal volume of urine is about 1 L / day.

Both BUN & plasma creatinine increase when GFR decreases.

GFR decreases with age, although plasma creatinine remains constant because of decreased muscle mass.

3- Filtration fraction

It is ratio of GFR to renal plasma flow.

Normal value: 0.16 – 0.20 i.e. 16 % to 20 %.

Glomerular membrane:

- It is formed of 3 layers

1) Capillary endothelium:

It has small holes (70 – 90 nm).

It does not act as a barrier against plasma protein filtration.

2) Basement membrane:

It is meshwork of collagen and proteoglycan fibrillae that has large spaces.

The proteoglycan carry strong negative charges which prevent the filtration of plasma proteins, but filters large amount of H₂O & solutes.

3) Podocytes:

They are epithelial cells that line the outer surface of the glomerulus.

They have numerous pseudopodia that interdigitate to form slit pores (25 nm wide).

Mesangial cells:

. They are stellate cells located between the basement membrane and the endothelium at bifurcation of the capillaries.

. They are contractile cells.

Functions of mesangial cells:

- 1- Regulate GFR i.e. when contract will reduce filtration area.
- 2- Take up immune complexes → production of glomerular diseases.

-Surface area of glomerular membrane = 0.8 m²

-Permeability of the glomerular membrane:

It is 50-times that of skeletal muscles capillaries.

It is highly selective.

This selectivity is determined by:

1) Size of the molecule:

Filtration is inversely proportional to diameter between 4 – 8 nm.

Less than 4 nm, the molecules are freely filtered.

More than 8 nm, the molecules are not filtered.

2) Charges of the molecules:

Negatively charged molecules e.g. albumin (7 nm) is filtered less easily than positively charged molecules of equal size.

Only 0.2 % of albumin plasma is filtered.

Note:

In some kidney diseases, the negative charges of the basement membrane are lost → albuminuria (pore size are kept constant).

Measurement of GFR:

1) Inulin clearance:

Inulin is a polymer of fructose of MW 5200 found on dahlia tubers.

Inulin has the following characteristics:

1- Freely filtered i.e. plasma conc. = filtrate concentration.

2- Not reabsorbed or secreted by renal tubules.

i.e. Amount filtered per min. = amount excreted in urine / min.

3- Not metabolized.

4- Not stored in the kidney.

5- Dose not affect filtration rate.

6- Its concentration is easily measured.

Steps:

1- A loading dose of inulin is intravenously injected, followed by sustained infusion to keep arterial plasma level constant.

2- After inulin has been equilibrated in body fluids, urine and plasma samples are taken where inulin concentration is measured.

Calculation:

Amount filtered / min = Amount excreted / min.

So, $C_{in} \times P_{in} = V \times U_{in}$ i.e. $C_{in} = \frac{V \times U_{in}}{P_{in}}$

P_{in} = inulin concentration in plasma (same conc. in filtrate).

U_{in} = inulin conc. in urine.

V = Volume of urine per minute.

C_{in} = volume filtered / minute i.e. GFR i.e. inulin clearance (refer to plasma clearance).

Example:

Plasma inulin concentration = 2 mg/ml, volume of urine in 2 hours = 120 ml & inulin concentration in urine = 240 mg/ml.

$$\text{GFR} = \frac{240 \times 1}{2} = 120 \text{ ml/minute}$$

II) Creatinine clearance

Advantage:

Creatinine is an endogenous substance formed from muscle creatine i.e. no extrawork is added to kidney.

Characters of creatinine:

- 1- Freely filtered.
 - 2- Not reabsorbed.
 - 3- Partially secreted by renal tubules.
- Error caused by the partial secretion is cancelled because:
- $\frac{U_{cr} \times V}{P_{cr}}$ is high as a result of partial secretion.
 - P_{cr} is also high as a result of nonspecific chromogens.

III) Radio isotopes as ^{51}Cr - EDTA.

Forces (factors) that control GFR:

The same factors governing filtration across any capillary:

- 1- Hydrostatic pressure gradient across capillary wall (filtering).
- 2- Osmotic pressure gradient across capillary wall (opposing).
- 3- Permeability of the glomerular capillaries.
- 4- Effective filtration surface area.

Forces favoring filtration:

- 1- Hydrostatic pressure in glomerular capillary, $HP_{GC} = 60 \text{ mmHg}$.
- 2- Osmotic pressure of proteins in the filtrate, $\pi_{BC} = 0 \text{ mmHg}$.

Forces opposing filtration:

- 1- Hydrostatic pressure in Bowman's capsule $HP_{BC} = 18 \text{ mmHg}$.
- 2- Osmotic pressure of plasma proteins in glomerular capillary, $\pi_{GC} = 32 \text{ mmHg}$.

The net filtering pressure = $60 - 50 = 10 \text{ mmHg}$.

These factors are summarized by the Starling equation:

$$\text{GFR} \propto (HP_{GC} + \pi_{BC}) - (HP_{BC} + \pi_{GC})$$

$$\text{GFR} = K_F (HP_{GC} + \pi_{BC}) - (HP_{BC} + \pi_{GC})$$

K_F depends on:

- 1) Permeability of the glomerular membrane.
- 2) Surface area of the glomerular capillaries.

As $GFR = K_F$ (net filtering pressure)

$$K_F = \frac{GFR}{\text{net filtering pressure}}$$
$$= \frac{125}{10} = 12.5 \text{ ml / min / 1 mmHg}$$

i.e. K_F is the GFR per one mmHg of filtration pressure.

Factors that affect GFR:

Factors involved in Starling equation

I) Changes in ultrafiltration coefficient (K_F)

i.e. $++ K_F \longrightarrow ++ GFR$ & vice versa.

K_F is affected by:

- 1) Permeability of the glomerular membrane:
 $++$ thickness of glomerular capillary membrane $\longrightarrow --$ permeability
e.g. in chronic uncontrolled diabetes mellitus & hypertension.

- 2) Surface area of the glomerular capillary

a- Contraction of mesangial cells will reduce the surface area $\longrightarrow -- GFR$.

e.g. ADH (vasopressin), Norepinephrine, Thromboxane A₂, Leucotrienes A & D, PGF₂, endothelins and Histamine.

b- Relaxation of mesangial cells $\longrightarrow ++ GFR$.

e.g. ANP, PGE₂, cAMP & Dopamine.

c- Some diseases e.g. chronic uncontrolled diabetes mellitus reduce the surface area by $---$ number of functional glomerular capillaries.

II) Changes in glomerular hydrostatic pressure:

Factors that determine the glomerular hydrostatic pressure:

- 1- Diameter of the afferent arterioles:

e.g. bradykinin, PGE₂ and PGI₂

b- VC of afferent arterioles e.g. $++$ sympathetic activity during exercise

$-- HP_{oc} \longrightarrow -- GFR$ to less than 50% of normal.

- 2- Diameter of the efferent arterioles:

a- Moderate VC $\longrightarrow ++ HP_{oc} \longrightarrow$ slight $++$ of GFR e.g. angiotensin II.

b- Severe VC $\longrightarrow -- RBF \longrightarrow -- GFR$.

3- ABP

- Between 90 & 200 mmHg: GFR & RBF are kept relatively constant by autoregulatory mechanisms.
- Below 75 mmHg, there is a sharp drop in GFR.

Mechanism of autoregulation:

a- Myogenic autoregulation:

This mechanism is rapid & it is 1st line of defense:

- An increase in ABP: discussed page 4.
- A decrease in ABP $\longrightarrow$ VD (relaxation) of afferent arterioles.

b- Tubulo-glomerular feedback:

- ++ ABP $\longrightarrow$ ++ RBF & GFR $\longrightarrow$ ++ delivery of solute & H₂O to macula densa which secretes adenosine & i.e. vasoactive substance $\longrightarrow$ VC of afferent arterioles $\longrightarrow$ -- RBF & GFR to normal.

- -- ABP $\longrightarrow$ -- RBF & GFR $\longrightarrow$ ++ reabsorption of Na⁺ & CL⁻ in the ascending loop of Henle $\longrightarrow$ -- delivery of NaCl to macula densa which sends signal causing:

1) VD of afferent arteriole $\longrightarrow$ ++ HP_{GC} that return GFR towards normal.

2) VC of efferent arteriole due to renin release from juxtaglomerular cells that ++ RBF & GFR to normal.

III) Changes in Bowman's capsule hydrostatic pressure

++ HP_{BC} e.g. stone in ureter $\longrightarrow$ -- GFR & vice versa.

IV) Changes in glomerular colloidal osmotic pressure

- ++ π_{GC} e.g. in dehydration $\longrightarrow$ -- GFR.

- -- π_{GC} e.g. in hypoproteinemia $\longrightarrow$ ++ GFR.

Other factors:

V) Renal vasodilators:

e.g. PGE₂, PGI₂ and bradykinin $\longrightarrow$ ++ RBF & GFR

So, aspirin which blocks PG synthesis $\longrightarrow$ -- GFR.

PGs synthesis in kidneys is increased by hemorrhage (due to sympathetic stimulation and ++ angiotensin II); This may protect the renal vessels from severe VC.

VI) Protein intake $\xrightarrow{++\text{protein intake}}$ ++ amino acids in glomerular filtrate $\longrightarrow$ ++ amino acids reabsorption in PCT $\longrightarrow$ ++ Na reabsorption in PCT $\longrightarrow$ -- NaCl delivered to macula

densa which sends signals causing VD of afferent arterioles & VC of efferent arterioles $\longrightarrow$ ++ GFR i.e. tubulo-glomerular feedback.

Tubular processing of the glomerular filtrate

Urinary excretion rate = filtrate rate – reabsorption rate + secretion rate.
Magnitude of tubular processing is shown in this table

Substance	Concentration in urine (U)	Concentration in plasma (P)	U / P ratio
Glucose mg / dl	0	100	0
Na ⁺ mEq / L	90	150	0.6
Urea mg / dl	900	15	60
Creatinine mg / dl	150	1	150

Tubular reabsorption

It involves transport

- 1- From lumen across tubular epithelium to renal interstitial fluid.
- 2- From the interstitial fluid into the peritubular capillaries.

Types of transport across the tubular epithelium:

- 1- Trans-cellular through cells
- 2- Para-cellular through the tight junctions between the cells.

Mechanism of tubular transports:

A) Active transport against electrochemical gradient

1- Primary active transport:

It requires energy directly from ATP.

ATPase is a component of a carrier (transporter).

Example: Na⁺ reabsorption in PCT.

- **At the basolateral border of tubular epithelium:**

Na⁺ - K⁺ ATPase pump:

Extrudes 3 Na⁺ ions into the interstitium in exchange for 2 K⁺ ions that are pumped into the cell; this decreases intracellular Na⁺ conc. and creates a -ve potential -70 mV inside the cell.

- **At the luminal border:**

Na⁺ diffuses from the lumen to the cell along electro-chemical gradient.

2- Secondary active transport

It dose not require energy direct from ATP.

i- Co-transport:

Two substances bind to a specific carrier & are cotransported in one direction:

One substance diffuses along its electrochemical gradient;

Second substance is transported against its electrochemical gradient.

e.g. secondary active transport of glucose

ii- Counter-transport:

Two substances bind to a specific carrier & are transported in two directions:

e.g. secondary active secretion of H^+ .

B) Passive reabsorption:

1- Passive reabsorption of chloride:

The transport of Na^+ ions out of the lumen leaves the lumen negatively charged. This causes Cl^- ions to diffuse passively via paracellular pathway.

2- Osmosis of water:

Water follows NaCl by osmosis via paracellular pathway.

3- Passive reabsorption of urea (back diffusion of urea):

As a result of H_2O reabsorption, the urea concentration in the lumen is increased. About 50 % of the filtered urea undergoes back diffusion from the lumen to blood.

C) Pinocytosis:

It is an active transport mechanism for reabsorption of proteins and peptides in the proximal convoluted tubules.

Tubular transport maximum:

Substances that are actively reabsorbed or secreted require a specific transport system i.e. specific carrier & enzymes.

So, they exhibit transport maximum when the carrier system becomes saturated as the tubular load is increased.

Solutes that exhibit T_m limited reabsorption:

e.g. glucose, amino acids, phosphates and sulphates.

- Substances that have reabsorption maximum have a threshold concentration in plasma below which none of the substance appears in urine & above which progressively large quantities appears in urine.

Substances that exhibit T_m limited secretion:

e.g. para-amino hippuric acid (PAH) and penicillin

- The affinity of the transport system for secreted substances is so high that essentially all the substance is secreted into the lumen so long as the transport system is not saturated.

Gradient-time transport

Substances that are reabsorbed by diffusion do not exhibit T_m . Instead, transport is termed gradient-time transport. It depends on:

- 1- The electrochemical gradient for the substances across the membrane.
 - 2- The time the substance remains in the lumen i.e. tubular flow rate.
- Some actively transported substances also obey the gradient-time transport e.g. Na^+ reabsorption in PCT:
- a- The greater the concentration of Na^+ in the proximal tubule, the greater the reabsorption rate.
 - b- The slower the flow rate of the tubular fluid, the greater the percentage of Na^+ that can be reabsorbed from the proximal tubule.

Absorption by the peritubular capillaries:

The forces that act across the peritubular capillaries:

1) Forces that favor reabsorption:

- a- The colloidal osmotic pressure of peritubular capillaries = 32 mmHg.
- b- The hydrostatic pressure in renal interstitium = 6 mmHg.

2) Forces that oppose reabsorption:

- a- The hydrostatic pressure inside peritubular capillaries = 13 mmHg.
- b- The colloidal osmotic pressure of renal interstitium = 15 mmHg.

$$\text{Net reabsorptive force} = (32 + 6) - (13 + 15) = 10 \text{ mmHg.}$$

Sodium handling by the renal tubules

Na^+ reabsorption in different segments of renal tubule:

- 96 % to 99 % of the filtered Na^+ is reabsorbed.
- Na^+ is actively reabsorbed in all portions of the tubule except in the thin descending & ascending part of loop of Henle.
- 90 % of the energy consumed by the kidney is used for active transport of Na^+ .
- The reabsorption of Na^+ is coupled with:
 - a- Reabsorption of most of the solutes in the filtrate by secondary active mechanism or by dilution.
 - b- Reabsorption of water by osmosis.

c- Secretion of H^+ & K^+ .

1) In the Proximal tubule:

65 % of the filtered Na^+ is reabsorbed by the proximal tubule.

It is active process & it depends on $Na - K$ pump at the basolateral border to keep low intracellular Na^+ concentration.

Although Na^+ reabsorption is active in PCT, it has no tubular maximum, but it obeys **gradient – time transport** (see before page 13).

A- In the first half of the proximal tubule:

Na^+ reabsorption is accompanied by **cotransport** of glucose, amino acids, sulphates, phosphate, organic acids (lactate & citrate) & bicarbonate.

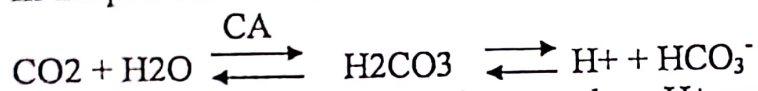
B- In late half of the proximal tubule:

Na^+ reabsorption is accompanied by chloride ions.

Reabsorption of Na^+ across the luminal border is accompanied by H^+ secretion via $Na^+ - H^+$ **counter- transport**.

H^+ secretion is accompanied by HCO_3^- reabsorption:

In the proximal tubule cell:



H^+ is secreted into the tubular lumen, where H^+ combines with filtered HCO_3^- to form $CO_2 + H_2O$ under the effect of carbonic anhydrase in the luminal membrane.

For each H^+ ion that is secreted, one HCO_3^- ion generated within PCT, then HCO_3^- is transported across the basolateral border to the peritubular capillaries.

2) In loop of Henle and early distal tubule:

a- Thin descending limb:

It reabsorbs water.

Na^+ is not reabsorbed (no protein channels for Na^+ at the luminal border).

b- Thick ascending limb and early distal tubule:

25% of the filtered load of Na^+ , K^+ and Cl^- are reabsorbed by cotransport mechanism that cotransport one Na^+ , one K^+ and two Cl^- from the lumen into the cells.

Most of the K^+ enters the cell refluxes back into the lumen via K^+ channels and serves two functions:

- i- It ensures enough concentration of K^+ for cotransporter.
- ii- The resulting net positive potential in the lumen facilitates paracellular reabsorption of several cations including Na^+ , K^+ , Ca^{++} and Mg^{++} .

c- Thin ascending limb

NaCl is passively reabsorbed by concentration gradient.

Bartter's syndrome:

- **Cause:** defect in the $\text{Na}^+ - \text{K}^+ - 2 \text{Cl}^-$ cotransporter in the luminal membrane of the thick ascending limb.
- **Effect:** renal salt wasting, volume depletion, hypercalciuria, hypokalemia & metabolic acidosis.

3) Late distal tubule and collecting duct

Less than 10 % of filtered Na^+ is reabsorbed by principal cell through Na^+ channels at the apical membrane. The anion that accompanies Na^+ is Cl^- . The reabsorption of Cl^- is paracellular and is driven by the luminal negative potential that results from Na^+ reabsorption.

Regulation of Na^+ excretion

Na^+ salts accounts for over 90 % of osmotically active solutes in plasma and interstitial fluid.

Na^+ excreted = Na^+ intake = 1 mEq up to 400 mEq / day.

Na^+ excretion depends of the amount filtered & reabsorbed.

So, Na excretion depends of factors affecting GFR & tubular reabsorption:

1) Glomerulo-tubular balance:

Definition: $++ \text{ GFR} \longrightarrow ++ \text{ reabsorption of solutes and in turn, } \text{H}_2\text{O}$.

Site: PCT (main site) and loop of Henle.

It can occur in isolated kidney independent of hormones.

It is prominent for Na^+ so, the renal tubules reabsorb a constant percentage of the filtered Na^+ rather than a constant amount.

Importance:

- a- It prevents overloading of distal tubular segment when GFR is increased.

b- It prevents losses of Na^+ and water in urine that may result from sudden increase in GFR.

2) Rate of tubular flow:

Slow rate of flow e.g. -- GFR $\longrightarrow$ ++ Na^+ tubular reabsorption.

3) Pressure natriuresis & pressure diuresis:

It is neither nervous nor hormonal

++ ABP $\longrightarrow$ ++ Na^+ excretion $\longrightarrow$ -- ECF volume.

Mechanisms:

a- Decreased angiotensin II secretion.

b- Back leak of Na^+ into the tubular lumen due to:

i. Rise of the hydrostatic pressure in the peritubular capillaries due to rise of ABP.

ii. Rise of the interstitial fluid hydrostatic pressure due to rise of the hydrostatic pressure in the peritubular capillaries.

This results in reducing the net absorption of Na^+ & water $\rightarrow$ +++ urine output.

4) Hormonal control

a- Mineralocorticoids e.g. Aldosterone

They act on P cells to ++ Na^+ reabsorption in exchange with K^+ or H^+ .

- They ++ No of Na^+ channels in apical membrane of P cells.
- They ++ No of $\text{Na}^+ - \text{K}^+$ ATPase molecules in the basal membrane.

b- Glucocorticoids have weak mineralocorticoids activity.

c- Angiotensin II most powerful Na^+ retaining hormone by direct action of PCT & via aldosterone.

- ++ aldosterone secretion.
- Direct action on PCT stimulates $\text{Na}^+ - \text{K}^+$ and $\text{Na}^+ - \text{H}^+$ pumps.
- Constrict efferent arteriole which -- hydrostatic pressure & ++ oncotic pressure in peritubular capillaries.

d- Estrogen: ++ Na^+ reabsorption.

e- ANP ++ NaCL & H_2O excretion via:

i- ++ GFR by:

- Relaxation of the mesangial cells $\longrightarrow$ ++ area of filtration.
- VD of afferent and VC of efferent arterioles.

ii- -- renin secretion.

iii- -- Na^+ reabsorption by collecting tubule by direct action:

- Inhibit Na^+ channels in the apical membrane.
- Inhibit $\text{Na}^+ - \text{K}^+$ ATPase in the basolateral membrane.

f- PGE_2 -- Na^+ reabsorption by direct effect as that of ANP.

g- Endothelins ++ PGE_2

5) Sympathetic stimulation

It -- Na^+ excretion via:

- ++ Na^+ reabsorption in PCT & thick ascending limb of loop of Henle.
- ++ Renin secretion $\longrightarrow$ ++ angiotensin II.
- -- GFR by constricting renal vessels.

6) Diuretics:

It ++ Na^+ excretion (see later)

Glucose reabsorption by the renal tubules

- Complete reabsorption (only few mg appear in urine per 24 hours).
- Site: early portion of the proximal convoluted tubules.
- Secondary active reabsorption i.e. cotransport with Na^+ .

Mechanism:

A) At luminal border:

- Cotransport with Na^+ :

The glucose & Na^+ bind to a common carrier SGLT_2 (sodium – dependent glucose transport).

As Na^+ moves down its electrochemical gradient, glucose is carried into the cell.

- This transport is Na^+ dependent.
- This transport can be blocked by:
 - . Oubain: blocks $\text{Na}^+ - \text{K}^+$ ATPase.
 - . Phlorhizin: competes with glucose for SGLT_2 carrier.

B) At the basolateral border:

- Glucose is carried into the interstitium by facilitated diffusion. The carrier is GLUT_2 (glucose transporter).
- This transport is Na^+ independent.
- The carrier is phlorhizin insensitive.

Notes:

- Fasting blood glucose level: 70 – 110 mg %.
- Renal threshold for glucose: plasma level at which glucose first appears in urine in more than the normal minute amount.

Value: arterial blood 200 mg / dl.

Venous blood 180 mg / dl.

- **Tubular maximum for glucose (T_mG):** the maximum amount of glucose (in mg) that can be reabsorbed per minute.

It is an indication of the reabsorption capacity of the kidney.

It is determined by the number of glucose carrier in PCT.

Value: 300 mg / min in female; 375 mg / min in male.

- **Glucose titration curve and T_m:**

It depicts the relation between plasma glucose concentration & glucose reabsorption.

The filtered load & the excretion rate of glucose are plotted on the same graph.

The curve is done experimentally by infusion of glucose and measuring its rate of reabsorption as the plasma conc. is increased.

It is best understood by examining each relationship separately and then considering all three relations together.

1- **Filteration load** = GFR x (P) glucose (linear relation).

2- **Reabsorption:** at plasma glucose concentration:

- Below 200 mg / dl: all filtered glucose is reabsorbed i.e. reabsorption equals filtration.

- 200 to 300 mg / dl: the reabsorption curve bends as some of the filtered glucose is not reabsorbed.

- Above 300 mg / dl: the reabsorption reaches its maximum as the carriers are completely saturated.

3- **Excretion:** at plasma glucose concentration:

- Below 200 mg / dl (renal threshold): none is excreted.

- 200 to 300 mg / dl: some of the filtered glucose is excreted.

- Above 300 mg / dl (T_mG): the curve for excretion now increases linearly paralleling that for filtration.

Splay is that portion of the titration curve where reabsorption is approaching saturation but it is not fully saturated.

Splay is the region of the absorption curve between threshold & T_m & occurs between plasma concentration of about 200 & 300 mg/ dl

Explanation: Splay is due to heterogeneity of T_m in different nephrons.

T_m for the whole kidney reflects the average T_m of all nephrons.

Some nephrons will reach T_m at a lower plasma glucose concentration than others, so T_m is approached gradually rather than sharply.

- **Glycosuria** = excretion of glucose in urine in considerable amounts.

It leads to osmotic diuresis with loss of Na⁺ and K⁺.

Causes:

- 1- Diabetes mellitus: blood glucose level > renal threshold.
 - 2- Renal glycosuria: renal threshold < normal blood glucose level.
- It is caused by congenital defect in the glucose transport mechanism.
TmG is also markedly decreased.

Water reabsorption and excretion of water

The same load of solute is excreted per 24 hours in:

- Urine volume of 500 ml with concentration 1200 - 1400 mOsm / liter.
- Or urine volume of 23.3 L with concentration 300 mOsm / liter.

Thus it is the water load which is changed i.e. regulated by ADH (vasopressin) acting on the collecting ducts.

Water reabsorption:

It is a passive process throughout the whole nephron.

Water reabsorption is of two types:

1) Obligatory H ₂ O reabsorption.	2) Facultative H ₂ O reabsorption.
- 87 % of filtered H₂O. - Independent of ADH. - Secondary to solute reabsorption by osmosis, so no change in tubular fluid osmolality. - In the following segments: 1- PCT 65 % 2- Loop of Henle 15 % 3- 1st half of DCT 5 % 4- Collecting duct 2 %	- About 13 % of filtered H₂O. - Controlled by ADH. - Independent of solute reabsorption so, it changes urine concentration (osmolality). - In the following segments: 1- Late DCT 2- Cortical collecting tubule. 3- Medullary duct.

PCT contains aquaporin - 1 (water channels) in the luminal membrane.

Urine concentration & dilution:

The final urine volume and osmolality depends only on the extent of facultative water reabsorption (solute load is constant).

Renal mechanism for excreting concentrated urine:

- 1) High ADH level.
- 2) Hyperosmotic gradient of renal medulla.

Hyperosmotic gradient of interstitium of renal medulla:

- 300 mOsm / L in the superficial layer of the medulla.
- 1200 mOsm / L in the deep layer in the tip of the papillae.

Mechanisms that produce hyperosmotic gradient include:

- 1- The counter current multiplier system of loop of Henle of the Juxta medullary nephron.
- 2- The counter current exchange system of the vasa recta.
- 3- Diffusion of large amount of urea from the medullary collecting ducts into medullary interstitium.
- 4- Sluggish medullary flow 1 –2 % of RBF.

This minimizes solute loss from the medullary interstitium.

Counter current system is a system in which the inflow runs parallel to, counter to and close to the outflow for some distance.

Two types:

- 1- The counter current **multiplier** creates the medullary hyperosmolality.
- 2- The counter current **exchange** maintains the medullary hyperosmolality. I.e. the vasa recta prevent it from being dissipated.

Counter current multiplier (Loop of Henle):

- Ascending limb

a) Thick segment:

It is absolutely impermeable to H_2O

Na^+ , K^+ and Cl^- are cotransported at the luminal border dependent on $Na^+ - K^+$ ATPase pump at the basolateral border.

Considerable amount of Ca^{++} , Mg^{++} & HCO_3^- are also reabsorbed.

b) Thin segment:

NaCl is passively reabsorbed into the medullary interstitium i.e. along their concentration gradient.

Result: the tubular fluid becomes hypotonic 100 mOsm / L as it enters the distal tubule.

Note: Earle distal tubule is relatively impermeable to water. Continued removal of solutes further dilutes the tubular fluids (about 60 mOsm/ liter).

- Descending limb

Very permeable to water.

Much less permeable to NaCl and urea.

Therefore, the tubular osmolarity gradually rises from 300 to 1200 mOsm / L at the tip of the loop due to:

- i- Osmosis of H_2O out of the descending limb.
- ii- Diffusion of NaCL from the medullary interstitium into the descending limb.

- The interstitium fluid makes osmotic equilibrium with the descending limb being H_2O permeable.

Thus the interstitial fluid forms a hyperosmotic gradient starting from 300 mOsm /L at superficial layers of medulla & reaches 1200 mOsm / L at deep layers of the medulla.

Counter current exchange (Vasa recta):

- In the descending limb of the vasa recta:

a- Solutes diffuse from the medullary interstitium to the blood along concentration gradient.

b- Water diffuses from the blood to the medullary interstitium.

Result: At the tip of vasa recta blood osmolarity = 1200 mOsm / L

- In the ascending limb of the vasa recta

a- Solutes diffuse back to the medullary interstitium.

b- Water diffuses from the interstitium to the blood.

Functions of vasa recta:

It maintains hyperosmotic gradient via:

1- Trapping solutes (NaCL and urea) in the renal medulla.

2- Removal of water reabsorbed from interstitium back to the general circulation by the usual colloid & hydrostatic pressure.

Contribution of urea to hyperosmotic gradient of medullary interstitium:

Urea contributes 40 % of the osmolality i.e. 500 mOsm / L. thus plays an important role in the process of urine concentration.

- A high protein diet increases the ability to concentrate the urine.
- Protein deficiency impairs the ability to concentrate the urine.

Handling of urea by the renal tubule:

1) PCT

40 % of filtered urea is passively reabsorbed.

Mechanism H_2O reabsorption in PCT $\longrightarrow$ ++ urea conc. in lumen.

2) Thick ascending limb of loop of Henle, DCT & cortical collecting tubules:

- All are relatively impermeable to urea.

- H_2O reabsorption in DCT & cortical collecting tubule (in presence of ADH $\longrightarrow$ ++ urea conc. In tubular fluid.

3) Inner medullary portion of the collecting duct

Urea diffuses into the medullary interstitium to ++ its osmolality.

Diffusion of urea is facilitated by ADH.

40 – 60 % of the tubular load of urea is excreted in urine.

Urea excretion is increased by:

- 1- ++ GFR.
- 2- ++ plasma urea level.

Urea cycle:

Urea moves from the medullary interstitium into the thin loop of Henle and back down into the medullary collecting duct & again to medullary interstitium several time before urea is excreted.

Role of ADH:

a- Late distal tubule and cortical collecting tubules:

ADH ++ their permeability by insertion of aquaporin2 water channels into the luminal border of the principal cells $\longrightarrow$ reabsorption of up to 8 % of filtered H_2O out of the hypotonic fluid entering this segment and the tubular fluid becomes iso- osmotic.

b- Inner medullary duct:

ADH ++ their permeability (aquaporin2 water channels) $\longrightarrow$ reab. of 4.7 % of the filtrate and tubular fluid becomes hyperosmotic having the same concentration of the interstitium (maximum 1200 mOsm).

Renal mechanism for excreting diluted urine:

Glomerular filtrate has the same osmolarity of plasma (300 mOsm).

To excrete diluted urine, solutes are reabsorbed to a greater extent than water in the following segments:

- 1) Ascending limb of loop of Henle
- 2) Distal tubule, cortical collecting duct & medullary collecting duct.

In absence of ADH, they are impermeable to H_2O .

Reabsorption of NaCL continues, so the tubular fluid becomes more diluted with minimal osmolarity.

Disorders of urinary concentration

Diabetes insipidus: DI

- **Types and causes:**

1- **Central DI:**

-- ADH secretion due to lesion of hypothalamus, hypothalamo-hypophyseal tract or posterior pituitary.

2- **Nephrogenic DI:**

Congenital defect in V2 receptors in the collecting duct.

- **Symptoms:**

1- **Polyurea:** ++ volume of diluted urine.

2- **Polydipsia:** Drinking of large amount of fluid.

If the sense of thirst is depressed e.g. by coma, these patients develop fatal dehydration.

Diuresis and diuretics:

Diuresis: is an increase in the rate of urine output.

Types:

1) **H₂O diuresis:**

It is caused by drinking large amount of water or hypotonic fluid. It begins after 15 minutes and reaches its maximum in 40 minutes.

Mechanism:

++ H₂O → -- OP → -- ADH → facultative H₂O reabsorption i.e. urine, large volume & hypotonic.

2) **Osmotic diuresis:** caused by the presence in filtrate of large quantities of unreabsorbable solute e.g. glucose or manitol.

Mechanism: unreabsorbable solute in PCT → obligatory H₂O reabsorption → -- Na⁺ concentration in tubular fluid →

-- Na⁺ reab. in ascending limb of loop of Henle → -- osmolarity of medullary interstitium → -- facultative H₂O reabsorption.

Urine is large in volume & iso or hypertonic.

Items	H ₂ O diuresis	Osmotic diuresis
<u>Cause:</u>	Ingestion of large amount of H ₂ O.	Presence of large amount of unreab. solute renal tubule.
<u>Solute excretion:</u>	Not increased.	Increased.
<u>ADH secretion</u>	Inhibited.	Normal or increased.
<u>-- H₂O reabsorption</u>	Facultative.	Obligatory & facultative.
<u>Maximal urine flow.</u>	16 ml/min.	Large urine volume.
<u>Urine osmolarity</u>	Hypotonic	Isotonic or hypertonic.

3) Pressure diuresis.

4) Diuretic drugs 1, 2 & 3

- a- Ethanol (alcoholics): inhibit ADH secretion.
- b- Xanthenes (caffeine): ++ GFR & -- Na^+ reabsorption.
- c- Antagonists of V_2 vasopressin receptor: -- ADH action.
- d- Aldosterone inhibitors e.g. aldactone: -- $\text{Na}^+ - \text{K}^+$ exchange in DCT & collecting tubules $\rightarrow$ -- serum Na^+ & ++ serum K^+ .
- e- Carbonic anhydrase inhibitors e.g. acetazolamide (diamox) -- H^+ secretion $\rightarrow$ ++ Na^+ , K^+ and H_2O loss.
- f- Loop diuretics e.g. frusemide (lasix): inhibit $\text{Na}^+ - \text{K}^+ - 2 \text{Cl}^-$ cotransporter in the thick ascending limb of loop of Henle.

Tubular handling of K^+ by renal tubules

Rate of K^+ filtration = GFR X plasma K^+ level
= $180 \times 4.5 = 756 \text{ mEq / day}$.

K^+ reabsorption:

1) PCT:

Reabsorption of 65%.

2) Thick ascending limb of loop of Henle:

Reabsorption of 25 % actively cotransported with NaCl.

80 % of filtered load of K^+ is reabsorbed paracellular as a result of bulk flow with H_2O . 20 % is reabsorbed transcellular.

3) Collecting tubule:

5% is reabsorbed actively by intercalated cells by ATP dependent $\text{K}^+ - \text{H}^+$ antiporter at luminal membrane and then pass through K^+ channels in the basolateral membrane.

K^+ secretion:

In late distal & cortical collecting tubule, P cells secrete K^+ into the tubular lumen.

It is variable & depends on dietary K^+ , aldosterone level, acid- base status & urine flow rate

Mechanism of K secretion:

Under the effect of aldosterone:

- **At the basolateral membrane:** $\text{Na}^+ - \text{K}^+$ pump.

Na^+ moves into interstitium & K^+ moves into the cell.

The pump maintains a high intracellular K^+ concentration.

- **At the luminal membrane:** K^+ diffuses into the tubular fluid along its electrochemical gradient.

K^+ diffuses through K^+ channels & via $K^+ - Na^+$ cotransporter.

Regulation of K^+ secretion:

1) Plasma K^+ concentration:

Rate of K^+ secretion $\propto$ plasma K^+ concentration.

Mechanism:

a- $++$ activity of $Na^+ - K^+$ ATPase by $++$ ECF K^+ level (direct) and via aldosterone.

b- $++$ number of K^+ channel by aldosterone.

2) Flow rate in distal tubule

$++$ distal tubular flow rate e.g. by diuretic $\longrightarrow$ $-- K^+$ conc. in lumen
 $\longrightarrow$ $++ K^+$ gradient $\longrightarrow$ $++ K^+$ secretion.

This explains why diuretic therapy can lead to K^+ depletion.

3) Acid - base state

a- Metabolic acidosis (especially acute acidosis)

$-- K^+$ secretion.

Mechanism:

$--$ tubular cell concentration of K^+ caused by:

i- Inhibition of $Na^+ - K^+$ ATPase.

ii- Efflux of K^+ & uptake of H^+ by cortical collecting cells.

b- Metabolic alkalosis

$++ K^+$ secretion by opposite mechanisms.

4) Aldosterone increases K^+ secretion

Hyperaldosteronism increases K^+ secretion $\rightarrow$ hypokalemia & vice versa

Ca^{++} handling by renal tubules

Only plasma Ca^{++} not bound to plasma proteins (50 %) are filtered in kidney.

99 % of filtered Ca^{++} are reabsorbed by renal tubules.

1- PCT

65 % by passive reabsorption.

2- Loop of Henle (thick ascending limb)

25 – 30 % by passive reabsorption.

In 1 & 2, as Na^+ & H_2O are reabsorbed $\longrightarrow$ $++ Ca^{++}$ conc. in lumen
 $\longrightarrow$ Ca^{++} reabsorption.

3- DCT & collecting tubules

4 – 9 % are actively reabsorbed.

PTH stimulates Ca ATPase

Factors ++ Ca^{++} reabsorption	Factors -- Ca^{++} reabsorption
1- Increased PTH secretion. 2- 1-25 $(\text{OH})_2$ cholecalciferol. 3- Metabolic acidosis. 4- ++ plasma PO_4^{---} conc. via PTH. 5- -- ECF volume or ABP as Na^+ & H_2O reab. in PCT.	1- -- PTH secretion. 2- Calcitonin. 3- Metabolic alkalosis. 4- -- plasma PO_4^{---} conc.

Secretion of hydrogen and reabsorption of bicarbonate

H^+ is secreted in all parts of renal tubule except the descending and ascending thin limbs of loop of Henle.

For each H^+ ion secreted, one bicarbonate ion is reabsorbed.

Site	H^+ secretion	HCO_3^- reabsorption
1- PCT	85 %	85 %
2- Thick ascending loop of Henle.	10 %	10 %
3- DCT and collecting tubule.	5 %	4.9 %

The renal tubules are poorly permeable to HCO_3^- .

However, HCO_3^- which is reabsorbed is formed by the tubular cell from CO_2 .

- CO_2 formed by tubular cell or diffuses in from the blood.

Carbonic anhydrase dissociates

- $\text{CO}_2 + \text{H}_2\text{O} \longrightarrow \text{H}_2\text{CO}_2 \longrightarrow \text{H}^+ + \text{HCO}_3^-$.

- H^+ ions are secreted from tubular cell into the tubular fluid, where it is buffered by:

a- Bicarbonate buffer in the tubular fluid.

b- Phosphate buffer in the tubular fluid.

c- Ammonia synthesized by tubular epithelium.

Mechanisms of H^+ secretion:

Secondary active transport	Primary active transport
1- Site: PCT, loop of Henle & 1 st part of DCT. 2- Most of H^+ is secreted by this mechanism.	1- Late distal tubule and collecting tubule.

3- It is Na ⁺ dependent. 4- Counter transport mechanism. Antiport carrier at luminal border binds Na ⁺ and H ⁺ . - One H ⁺ is secreted. - One Na ⁺ & one HCO ₃ ⁻ are reabsorbed. 5- It is not stimulated by aldosterone.	2- It is Na ⁺ independent. 3- H ⁺ is transported actively by H ATPase pump at luminal membrane of intercalated cells. 4- It is stimulated by Aldosterone.
--	---

Fate of H⁺ secreted:

1) In the proximal convoluted tubule:

Buffering of H⁺ by NaHCO₃ in the tubular fluid.

$H^+ + HCO_3^- \rightarrow H_2CO_3$ (in the tubular lumen).

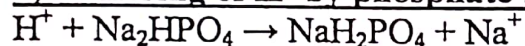
Na⁺ is reabsorbed in exchange with H⁺.

H₂CO₃ in the tubular lumen dissociates into H₂O & CO₂ by carbonic anhydrase at the luminal borders of tubular cells of PCT only.

pH of the tubular fluid of PCT is changed very little since most of H⁺ is removed from the tubular fluid by binding with HCO₃⁻

2) In the distal tubule & collecting duct:

a) Buffering of H⁺ by phosphate buffer:



Na⁺ is reabsorbed together with intracellular HCO₃⁻

NaH₂PO₄ is excreted in urine & accounting for most of the titratable acidity in urine.

Note:

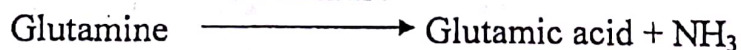
30 – 40 mEq of Na₂HPO₄ are available / day.

Na₂HPO₄ is concentrated by it reaches distal tubule & collecting duct.

b) Buffering of H⁺ by ammonia:

NH₃ is formed in most parts of the renal tubules specially the distal tubule & collecting duct from glutamine.

Glutaminase



NH₃ is lipid soluble & diffuses into the tubular fluid.

H⁺ combines with NH₃ to form NH₄⁺.

NH₄⁺ is excreted in urine together with CL⁻ (from NaCl) forming NH₄Cl.

Na^+ is reabsorbed to the renal interstitium together with HCO_3^- that formed in the tubular cells.

Importance of H^+ buffering:

H^+ secretion in the distal tubule & collecting duct occurs as long as pH of the fluid in these segments is above 4.5
pH of 4.5 is the limiting pH for H^+ secretion i.e. if the secreted H^+ is not buffered, pH of 4.5 would be reached rapidly leading to stoppage of further H^+ secretion.

Factors affecting acid secretion:

- 1- Aldosterone increases H^+ & K^+ secretion.
- 2- ++ intracellular PCO_2 (in respiratory acidosis) $\rightarrow$ ++ H^+ secretion.
- 3- K^+ excess in the cells inhibits H^+ secretion & vice versa.

Summary of Hormones that Act on the Kidney				
Hormone	Stimulus for Secretion	Time Course	Mechanism of Action	Actions on Kidneys
PTH	$\downarrow$ plasma $[\text{Ca}^{2+}]$	Fast	Basolateral receptor Adenylate cyclase $\rightarrow$ cAMP urine	$\downarrow$ Phosphate reabsorption (proximal tubule) $\uparrow$ Ca^{2+} reabsorption (distal tubule) Stimulates 1α hydroxylase (proximal tubule)
ADH	$\uparrow$ Plasma osmolarity $\downarrow$ Blood volume	Fast	Basolateral V_2 receptor Adenylate cyclase cAMP	$\uparrow$ H_2O permeability (late distal tubule and collecting duct principal cells).
Aldosterone	$\downarrow$ blood volume (via rennin-angiotensin II) $\uparrow$ plasma $[\text{K}^+]$	Slow	New protein synthesis	$\uparrow$ Na^+ reabsorption (distal tubule principal cells). $\uparrow$ K^+ secretion (distal tubule α -intercalated cells).
ANP	$\uparrow$ atrial pressure	Fast	Guanylate cyclase cGMP.	$\uparrow$ GFR $\downarrow$ Na^+ reabsorption
Angiotensin II	$\downarrow$ blood volume (via rennin)	Fast		$\uparrow$ Na^+ - H^+ exchange & HCO_3^- reabsorption (proximal tubule).

Plasma clearance: Renal clearance of a substance

- Definition:

It is the volume of plasma that is completely cleared of the amount of substance excreted in urine per minute.

- Calculation:

Amount cleared from plasma / min = Amount excreted in urine / min.

$$C \times P = U \times V$$

$$C = \frac{U \times V}{P}$$

C = volume of plasma cleared from a substance / min.

P = concentration of the substance per 1 ml plasma.

U = concentration of the substance per 1 ml urine.

V = volume of urine per minute.

- Importance of the determination of plasma clearance:

1) Study of tubular handling of different solutes in the filtrate:

Reabsorbed (glucose, urea, H₂O -- etc).

Secreted (creatinine, PAH --).

Substance	Tubular handling	Clearance ml / min
Inulin	Neither reabsorbed nor secreted.	125
Urea	Partially reabsorbed.	less than 125
Glucose	Completely reabsorbed.	0
PAH	Completely secreted.	650
Creatinine	Partially secreted.	125-650
Ammonia	Synthesized & secreted	more than 650

2) Measurement of GFR: (see before).

3) Measurement of the effective renal plasma flow: ERPF

The substance used is PAH (par amino hippuric acid) because:

- It is freely filtered by the glomerulus.
- It is completely secreted from the peritubular capillaries into the tubular lumen in a single circulation.

$$\text{ERPF} = \frac{U_{\text{PAH}} \times V}{P_{\text{PAH}}} = \text{about } 650 \text{ ml / minute.}$$

Measurement of the actual (total) renal plasma flow: TRPF

The extraction of PAH is 90 % i.e. only 90 % of PAH in renal arterial blood is removed in a single circulation. This is because only 90 % of RPF go to the nephrons.

$$RPF = \frac{ERPF \times 100}{90} = \text{about } 700 \text{ ml / min.}$$

Measurement of the actual (total) renal blood flow: TRBF

Knowing the haematocrite value (HV).

$$TRBF = \frac{RPF}{1 - HV} = \text{about } 1300 \text{ ml / minute.}$$

$$4) \text{ Calculation of filtration fraction} = \frac{GFR}{RPF} = 0.16 - 0.20$$

5) Free water clearance

It tests the power of the kidney to concentrate or dilute urine.

Free water is defined as distilled water that is free of solutes.

In the nephron, free water is generated in the diluting segment.

Measurement of free water clearance C_{H_2O} :

A) When ADH levels are low: all of the free water can not be reabsorbed by late DCT & collecting duct.

The urine is hypo-osmotic & free H_2O clearance is positive.

B) When ADH levels are high; all the free water is reabsorbed by late DCT and collecting duct.

The urine is hyperosmotic & free water clearance is negative.

The standard formula is not used to calculate free water clearance.

Free water clearance $C_{H_2O} = V - C_{osm}$ where,

$$C_{osm} = \text{total osmolar clearance} = \frac{V \times U_{osm}}{P_{osm}}$$

U_{osm} = urine osmolality.

P_{osm} = plasma osmolality.

V = urine flow rate.

Example:

If urine flow rate = 10 ml/ minute, urine osmolality is 100 mOsm/ L & plasma osmolality = 300 mOsm/ L

$$\text{Free water clearance } C_{H_2O} = V - C_{osm} = 10 \text{ ml/ minute} - 100 \times 10 / 300 \\ = 10 - 3.33 = + 6.67 \text{ ml/ minute}$$

6) Kidney function test: see later.

- Disadvantages: plasma clearance gives the net effect and not the detail study e.g. potassium clearance less than 125 i.e. partially reabsorbed (Net effect). Details: K^+ nearly completely reabsorbed then excreted.

Micturation

It is 2 main steps:

1- Filling of the bladder.

2- Micturation reflex: is a spinal autonomic reflex.

It is inhibited or facilitated by higher centers in CC & brain stem.

Physiological anatomy of the urinary bladder: 2 parts

1) Body:

Its smooth muscles are called detrusor muscle.

It acts as functional syncytium, when contract it ++ the pressure in the bladder to 40-60 mmHg.

2) Neck:

It is funnel shaped 2-3 cm long.

The internal urethral sphincter surrounds it, which is an extension of detrusor muscle.

Functions:

a- Its natural tone keeps the posterior urethra empty of urine therefore prevents emptying of the bladder until the pressure in the bladder body rises above a threshold level.

b- It prevents reflux of semen into the bladder during ejaculation. (Function of efferent sympathetic).

3) External urethral sphincter

It is a voluntary skeletal muscle.

It is used to control micturation consciously.

	Parasympathetic	Sympathetic	Somatic
Supplies	Wall of urinary bladder & inter. urethral sphincter.	Internal urethral sphincter.	External urethral sphincter.
Origin	S_2 & S_3	L_2	S_2 & S_3 .
Efferent	Pelvic nerve.	L. splanchnic nerve.	Pudendal nerve.
Ganglia	Terminal ganglia	Collateral ganglia	
Function	1- Contraction of the bladder wall. 2- Relaxation of	Prevent reflux of semen into bladder during	Voluntary control of external urethral

Afferent	internal urethral sphincter. 1- Detect degree of bladder stretch. 2- Of posterior urethra initiate reflex bladder emptying.	ejaculation. 1- Sensation of fullness. 2- Pain due to overstretch & infection.	sphincters. From stretch receptors in post. Urethra transmits sensation of urine flow to the urethra.
----------	---	--	--

Bladder filling:

The ureter course **obliquely** for several centimeters through the bladder wall & under mucosa.

The normal tone of detrusor muscle compresses the ureter and prevents reflux of urine in ureter.

Cystometrogram:

A plot of the intravesical pressure against the volume of urine in the bladder.

- 1) At intravesical pressure 0, there is no urine in the bladder.
- 2) Segment 1a: Pressure rises to 5-10 cm water by time; 50 ml of urine has collected.
- 3) Segment 1b: small additional rise in pressure with further increase in volume to 200-300 ml.

Laplace law explains this;

$$P = \frac{2T}{r}$$

As the bladder fills with urine, the tension in wall rises, but so does the radius. Therefore, the pressure increase is slight until the bladder is relatively full i.e. no r ++.

- 4) Segment II sharp rise at a volume of 400 ml.

The first urge to void is felt at a volume of 150 ml and marked sensation of fullness at a volume of 400 ml.

Micturation reflex:

- Stimulus: in adult, the volume of urine that initiates micturation reflex is 300-400 ml.
- Receptor: Stretch R in bladder wall & posterior urethra.
- Afferent: pelvic parasympathetic
- Efferent; pelvic parasympathetic.
- Response & effectors: detrusor muscle; contraction & internal urethral sphincter: relaxation.

. Micturation reflex is **self regenerative** i.e. once it begins, contraction of the bladder further activates the stretch receptors in bladder & posterior urethra → further ++ in reflex bladder contraction.

. Once the micturation reflex becomes powerful enough, it causes another reflex via pudendal nerve to inhibit external urethral sphincter.

Higher control of micturation reflex:

The reflex is controlled by **facilitatory and inhibitory higher centers:**

- Facilitatory centers:

a- Pontine centers.

b- Posterior hypothalamus.

- Inhibitory centers: midbrain.

- The cortical micturation center in the superior frontal gyrus.

It may facilitate or inhibit micturation reflex.

The higher centers exert final control of micturation so that:

- 1- They partially inhibit the reflex except when micturation is desired.
- 2- They can prevent micturation by contraction of ext. urethral sphincter.
- 3- When it is time to urinate, the cortical areas:
 - Facilitate the sacral center to initiate micturation reflex.
 - Inhibit the external urethral sphincter.

Mechanism by which voluntary micturation is initiated:

1) Relaxation of the pelvic floor muscles leads to downward tug on detrusor muscle to initiate its contraction.

2) Voluntary contraction of abdominal muscle increases intravesical pressure → entry of urine in bladder neck → stretch of the bladder neck → stimulate stretch receptors → excite micturation reflex.

3) Relaxation of external urethral sphincter.

After urination, the female urethra empties by gravity while the male urethra empties by contraction of the bulbocavernous muscle.

Abnormalities of micturation:

	<u>Deafferentiation</u>	<u>Denervation</u>	<u>Spinal cord damage</u>
<u>- Cause</u>	Damage of the dorsal root (tabes dorsalis)	Damage of the afferent and efferent nerves.	TS of spinal cord above sacral region.
<u>-Micturation reflex:</u>	Abolished	Abolished	Shock stage: lost Recovery stage; return
<u>-Voluntary control</u>	Lost	Lost	Lost
<u>- Bladder</u>	Thin wall, distended & hypotonic	Thick wall, shrunken & hyperactive.	Shock stage: flaccid. Recovery stage: hypertrophy with -- capacity.
<u>- Urination</u>	Bladder is full & overflows drops at a time by intrinsic response.	Hyperactive bladder expels dribbles of urine.	Shock stage: retention with overflow. Recovery stage: automatic bladder

Kidney function tests

1) Blood analysis

a- Blood urea

Normally = 20-40 mg / dl

It is a rough index being nonspecific test.

It varies with protein intake, liver diseases and renal perfusion.

b- Plasma creatinine

Normally = 0.6-1.5 mg / dl

It is a more accurate index, as it is produced from muscle at a constant rate; completely filtered & very little is secreted.

c- Plasma potassium

Normally = 3.5-5 mEq / L.

d- Inorganic phosphate

Normally = 2.6-4.5 mg / dl

e- Serum uric acid:

In male = 3.6-8.5 mg / dl.

In female 2.3-6.6 mg /dl

All the above values are ++ in renal insufficiency.

f- Blood pH:

Arterial = 7.4 & venous = 7.35

2) Urine analysis

a- Volume:

Normally = 500-1500 / day.

Polyurea: in diabetes mellitus, diabetes insipidus, H₂O diuresis, diuretics etc.

Oliguria: in dehydration and acute renal failure.

Anuria: in acute vascular thrombosis, total urinary obstruction.

b- Specific gravity:

Normally = 1010-1020

Low: in diabetes insipidus (DI).

High: in diabetes mellitus (DM).

Low fixed: at 1010 (= plasma) in chronic renal failure.

c- H₂O diuresis test:

It is done to test renal ability to dilute urine.

Person evacuates bladder then drinks 1.5 L water collect urine during the next 4 hours.

Normal results:

More than 800 ml urine, its specific gravity below 1003 & its osmolality below 80 mOsm / L.

It is non specific test as it is altered in adrenal hypofunction.

d- H₂O concentration test:

It is done to test renal ability to concentrate urine.

Person evacuates bladder then stop drinking for 12 hours.

Normal results:

Decreased urine volume.

Specific gravity of urine: 1025-1030

Osmolality of urine: above 900 mOsm.

It is altered in early renal diseases.

3) Tests depending on blood & urine analysis: plasma clearance

a- Creatinine clearance

It is used to measure GFR

So, changes reflect changes in GFR

b- PAH clearance

It is used to measure ERPF.

c- Urea clearance

It measures renal tubular function

Patient evacuates bladder then drinks glass of water:

- Calculate urine volume / minute.
- Determine urea concentration in urine and blood.

- Calculate the clearance value of urea using one of two equations depending on the volume of urine / min

Volume 2 ml or more / min	Volume less than 2 ml /min
Maximal urea clearance	Standard urea clearance
$C_m = \frac{U \times V}{P}$	$C_s = \frac{U \times \sqrt{V}}{P}$
Normally 70 ml / min	Normally 54 ml /min

The urea clearance is expressed as percentage of normal value.
 Below 5 % of normal indicates renal impairment.
 It is an early test, specific test & quantitative test.

4) Imaging techniques

a- Plain X ray:

It shows opaque calculi & calcifications.

b- Intravenous urography: using IV iodine dye e.g. diodrast.

Series of radiographs are taken at intervals after injection.

They show non opaque calculi, stricture of the urinary tract, dilated renal pelvis or non functioning kidney.

c- Ultrasonography

It shows renal size & position, tumor and cysts or dilatation of the collecting system in obstruction.

d- Computed tomography

It shows renal tumors or cysts.

Treatment of renal failure

1) Kidney transplants:

Kidney transplants in adult should:

- a- Raise post-operative GFR to 120 – 150 ml / min.
- b- Correct abnormal calcium homeostasis.
- c- Correct anemia.

N.B. receiving a kidney from a close relative has the highest chance of success.

2) Dialysis = diffusion of molecules via a semi-permeable membrane along their concentration gradient.

Methods of dialysis:

A) Kidney machine (hemodialysis):

The patient blood is directly cleaned as it passes through a **semi-permeable membrane tube** in contact with a balanced salt solution (dialysate).

Artificial kidney extracts waste products, toxic chemicals and drugs or adds substances to blood e.g. HCO_3^- if the blood is acidic.

In a course of 6 hours hemodialysis, 50 – 250 gm of urea is removed (more than urea clearance of normal kidneys).

Therefore, a patient needs undergo treatment only 2-3 times / week.

Patient blood is routed from an artery & is returned via a vein.

B) Continuous Ambulatory Peritoneal Dialysis (CAPD)

A fresh amount of dialysate is introduced directly into abdominal cavity from a bag attached to a permanently implanted tubule. Waste & water molecules pass into the dialysate from the surrounding organ before the fluid is collected four or eight hours later.

The patient can go about his activities during CAPD, unlike hemodialysis.

Dialysis fluid should:

- 1- Contain less K^+ than normal plasma.
- 2- Be buffered to prevent large changes in pH.
- 3- Be free of urea.
- 4- Be higher in osmolality than normal plasma to reduce ECF volume and arterial blood pressure.

ACID – BASE BALANCE (ACID – BASE STATE OF ECF)

Acid	Base
Molecule contributes H^+ to solution i.e. proton donor.	Molecule combines with H^+ in solute i.e. H^+ acceptor
a- Strong acid e.g. HCL	a- Strong base e.g. NaOH $\rightarrow$
Dissociation is complete 100 %.	$\text{Na}^+ + \text{OH}^-$ dissociation is complete 100%.
b- Weak acid e.g. H_2CO_3	b- Weak base e.g. $\text{NH}_4\text{OH} \xrightleftharpoons[99\%]{1\%} \text{NH}_4^+ + \text{OH}^-$
Dissociation is weak 1 %	Dissociation is weak 1 %

Free H^+ concentration in ECF is very low 0.00004 mmol / L (40 nmol / L).

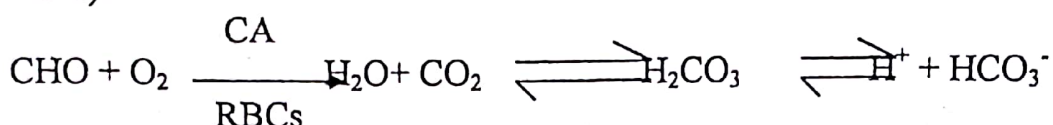
The H^+ concentration is kept constant by a balance between intake and output. This is because the protein mediated processes i.e. enzymes, transport molecules & contractile molecules depend on pH.

Sources of H⁺:

1- Ingested: some free H is ingested in food we eat.

2- Metabolism of food:

a- **CHO metabolism** generates 12000 – 20000 mmol/ day (volatile acids).



b- **Protein & lipid metabolism** generates 60 mmol / day (fixed acids).

They contain sulphate & phosphate, they metabolized $\longrightarrow$ H₂SO₄ & H₃PO₄

c- **Lactic acid** in severe exercise due to inadequate O₂.

d- **Ketoacids** (aceto-acetic & beta hydroxy butyric acid) in DM.

Amount of H⁺ in ECF is very small compared to amount of H⁺ produced / day.

pH is the minus log to base 10 of H⁺ concentration.

pH = - log₁₀ 0.00004 = 7.4 (slightly alkaline).

Death occurs, if pH falls below 6.8 or rises above 8.0.

Regulation of acid – base balance: 3 major systems:

1- The **buffer systems**: minimize the change in free H concentration.

2- The **respiratory system** removes H⁺ of volatile acids i.e. CO₂.

3- The **kidneys** remove fixed acids & restore ECF buffers.

BUFFER SYSTEMS

- A buffer is a molecule that **combines with or releases** a H⁺.

- It is composed of **weak acid** & salt of its conjugate base.

- The **combination** of all buffers **determines** the pH.

- **Henderson – Hasselbalch equation:**

$$\text{pH} = \text{pK} + \log_{10} \frac{[\text{salt}]}{[\text{acid}]}$$

pK : dissociation constant.

It is applied to any buffer, if its pK & concentration of its members are known.

Applying this equation to bicarbonate buffer:

pK = 6.1 [HCO₃⁻] = 24 mmol /L

[H₂CO₃] = PCO₂ x solubility coefficient (0.03).

$$\begin{aligned}\text{pH of arterial blood} &= 6.1 + \log_{10} \frac{0.03 \times 40}{1} \\ &= 6.1 + \log \frac{20}{1} = 6.1 + 1.3 = 7.4\end{aligned}$$

- The effectiveness of any buffer system depends on:

- a- Amount of the buffer pair.
- b- pK, the buffer is most effective when its pH = pK; because at this point the concentrations of the 2 members of the buffer are equal.

- Role of buffers in regulation of acid – base balance:

Buffers act within fraction of a second (immediate) to trap H temporarily until respiration & renal mechanisms act. They only **minimize** the change in pH.

- Types of chemical buffer systems

1- Bicarbonate buffer system $\frac{\text{H}_2\text{CO}_3}{\text{BHCO}_3}$ (B = Na or K)

2- Phosphate buffer system $\frac{\text{BH}_2\text{PO}_4}{\text{B}_2\text{HPO}_4}$

3- Protein buffer system:

- a- Plasma proteins.
- b- Hemoglobin.
- c- Tissue proteins.

Bicarbonate buffer system:

Disadvantages:

- a- Amount is not large 24 mmol / L.
- b- pK 6.1 far from pH of ECF (7.4).

Advantages:

Its 2 components can be physiologically controlled $[\text{HCO}_3^-]$ by kidneys and $[\text{H}_2\text{CO}_3]$ by respiratory system.

Thus, changes in pH that results from an alteration in either $[\text{HCO}_3^-]$ OR $[\text{H}_2\text{CO}_3]$ can be corrected by a similar change in the other component to preserve the buffer ration & in turn pH.

Factors that affect:

$[\text{HCO}_3^-]$
 $[\text{H}_2\text{CO}_3]$ i.e. PCO_2

Give rise to:

metabolic acidosis or alkalosis
respiratory acidosis or alkalosis

Phosphate buffer system:

It is a mixture of basic phosphate HPO_4^- & acidic phosphate H_2PO_4 .

Disadvantages: its amount in ECF is very low 1 mmol /L .

However, its concentration is high in ICF & tubular fluid (DCT).

Advantages: its pK 6.8 is near to pH of ECF (7.4).

Hemoglobin buffer

It plays an important role in CO_2 buffering.

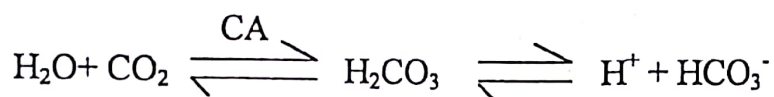
It has 6 times buffering power of plasma protein because:

- a- It is present in large amount (700 Hb in adult person).
- b- Each molecule of Hb contains 38 histidine residues.

Deoxyhaemoglobin is better buffer than oxyhaemoglobin.

Buffering of CO_2 (CL shift phenomenon):

- The CO_2 diffuses from the tissue cells into the RBCs, where:



Free H^+ combines with deoxygenated Hb & K^+ binds to HCO_3^- .

Some HCO_3^- ions diffuse to plasma to form $\text{Na}^+\text{HCO}_3^-$ to maintain electrical neutrality, Cl^- diffuses into the RBCs.

- At the lung, the process is reversed.

Thus, in chronic renal failure, -- Hb concentration which occurs in these patients contributes to their acidosis.

Intracellular buffers:

- They are mainly proteinate and organic phosphate.
- They can backup extracellular buffers as extracellular H^+ can exchange with Na^+ , K^+ , Ca^{++} and Mg^{++} . Thus, prolonged metabolic acidosis depletes cells of K^+ & bones of Ca^{++} .
- They are the most plentiful buffer of the body.
- They are much slower than extracellular buffers i.e. taking hours, because of the low permeability of the membrane of H^+ .

- Isohydric principle: The buffer systems buffer each other by shifting of hydrogen ions from one buffer to others.

Note: Acid -Base state is determined clinically by measuring in arterial blood of any two of these 3 measures:

- 1- $[\text{H}^+]$ 45 to 35 nanomolar (pH values 7.35 to 7.45)
- 2- PCO_2 35 to 45 mmHg.
- 3- $[\text{HCO}_3^-]$ i.e. alkali reserve 22 – 28 mEq / L

Respiratory control of acid – base balance

- Respiration control pH via controlling blood PCO_2 .

A decrease in pulmonary ventilation results in an increase in PCO_2 and $[\text{H}^+]$ i.e. -- pH and vice versa

- Mechanism of respiratory control of pH:

In metabolic acidosis, ++ $[\text{H}^+]$ stimulates respiratory centers via peripheral chemoreceptors $\longrightarrow$ hyperventilation $\longrightarrow$ PCO_2
 $\longrightarrow$ -- carbonic acid $\longrightarrow$ -- $[\text{H}^+]$.

e.g. $10 \text{ HCL} + 26 \text{ NaHCO}_3 \longrightarrow 10 \text{ NaCL} + 10 \text{ H}_2\text{CO}_3 + 16 \text{ NaHCO}_3$.

i.e. H_2CO_3 increases 10 mmol / l & NaHCO_3 decreases 10 mmol / L.

According to Henderson – Hasselbalch equation:

$$\text{pH} = 6.1 + \log \frac{26 - 10}{1.3 + 10} = 6.1 + \log \frac{16}{11.3} = 6.25$$

However, hyperventilation eliminates 10 mmol / L of carbonic acid so,

$$\text{pH} = 6.1 + \log \frac{16}{1.3} = 6.1 + 1.2 = 7.3$$

pH 7.3 is compatible with life (6.25 is incompatible).

In metabolic alkalosis, the reverse occurs.

Effectiveness of respiratory control:

- The respiratory control can return $[\text{H}^+]$ i.e. pH about 2/3 of the way back towards normal within **1-12 minutes** after acute disturbance in acid-base balance.
- The buffering power of the respiratory control is **1-2 times** as that of the entire chemical buffered combined.
- The respiratory control of the plasma pH has **limited ability** because the changes in PCO_2 have opposite on respiration.

Renal control of acid – base balance

It is the **most efficient** (powerful) mechanism.

It brings pH back to **normal** within **12 – 24 hours**.

(Refer to H^+ secretion & HCO_3^- reabsorption by the renal tubules).

ACID – BASE DISTURBANCE

pH depends on the ratio $\frac{[\text{HCO}_3^-]}{\text{PCO}_2}$

Acid – base disturbance is caused primarily by changes in either HCO_3^- or PCO_2 system.

This disturbance is corrected (compensated) by changes in the second system or both systems so that:

- The ratio $[\text{HCO}_3^-] / \text{PCO}_2$ & in turn pH returns to normal.
- However, $[\text{HCO}_3^-]$ & PCO_2 are both either increase or decrease.

Items	Respiratory acidosis	Metabolic acidosis
Arterial pH	Is less than 7.4 (7.35).	Is less than 7.4 (7.35).
Defect & causes.	++ arterial PCO_2 above 44 mmHg i.e. Hypoventilation. 1- Depression of respiratory center by narcotics or sedatives. 2- Paralysis of respiratory muscles. 3- Obstructive or restrictive lung diseases.	-- arterial HCO_3^- due to: 1- ++ <u>Fixed acids</u>: a- Diabetes mellitus. b- Shock: ++ lactic acid. c- Renal failure: -- excretion. d- Aspirin & methanol poisoning. e- ++ protein intake, H_2SO_4 & H_3PO_4. 2- -- <u>(loss) of HCO_3^-</u> a- Severe or prolonged diarrhea. b- Vomiting of intestinal content. c- Pancreatic fistula. d- Addison' disease.
Compensation	1- Chemical buffers. 2- Respiratory: limited valve. 3- Renal ++ HCO_3^- reabsorption.	1- Chemical buffers. 2- Respiratory stimulation -- PCO_2 3- Renal ++ HCO_3^- reabsorption.
Laboratory diagnosis	pH meter: -- pH	pH meter: -- pH.
- PCO_2	++	--
- HCO_3^- (alkali reserve)	++ > 28 mEq / L.	-- < 22 mEq / L.

Clinical diagnosis: - CNS - Respiration	Disorientation, drowsiness , coma & finally death Hypoventilation & cyanosis	Disorientation, drowsiness, coma & finally death. Hyperventilation.
--	--	--

Items	Respiratory alkalosis	Metabolic alkalosis
Arterial pH. Defect & causes.	Is more than 7.4 (7.45). -- arterial PCO_2 below 35 mmHg i.e. hyperventilation. 1- High altitude. 2- Psychological dyspnea & anxiety. 3- Fever. 4- Early in exercise. 5- Meningitis.	Is more than 7.4 (7.45). ++ arterial HCO_3^- due to: 1- Persistent vomiting of HCL while HCO_3^- is added to plasma. 2- Excess intake of alkali in treatment of peptic ulcer. 3- Diet rich in fruits & vegetables. 4- Cushing & Conn's syndrome: K^+ leaves cell in exchange with H^+ . 5- Diuretics except carbonic anhydrase inhibitors.
Compensation	1- Chemical buffers. 2- Respiratory: limited. 3- Renal: -- HCO_3^- reabsorption.	1- Chemical buffers. 2- Respiratory stimulation: ++ PCO_2 . 3- Renal:-- HCO_3^- reabsorption.
Laboratory diagnosis: - PCO_2 . - HCO_3^- (alkali reserve)	pH meter: ++ pH -- -- < 22 mEq/ L.	pH meter ++ pH ++ ++ > 28 mEq / L.